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CONTENTS

NUMBER 1, AUGUST, 1943

Recent Advances in the Chemistry of Complement. LOUIS PILLEMER... 1

The Reaction between Ethylene Derivatives and the Halogens. S. V. ANANTAKRISHNAN AND R. VENKATARAMAN... 27

NUMBER 2, OCTOBER, 1943

Thermal Analysis of Liquefied Gases. HAROLD SIMMONS BOOTH AND DONALD RAY MARTIN... 57

Alicyclic–Aromatic Isomerization. E. C. HORNING... 89

The Stereochemistry of Square Complexes. DAVID P. MELLOR... 137

NUMBER 3, DECEMBER, 1943

The Structure and Estimation of Natural Products Functionally Related to Nicotinic Acid. C. A. ELVEHJEM AND L. J. TEPLY... 185

The Hydroxamic Acids. HARRY L. YALE... 209

Polyhydric Alcohol Esters of Fatty Acids. Their Preparation, Properties, and Uses. H. A. GOLDSMITH... 257

RECENT ADVANCES IN THE CHEMISTRY OF COMPLEMENT[1]

LOUIS PILLEMER[2]

The Institute of Pathology, Western Reserve University, Cleveland, Ohio

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Complement is considered to be a chemical system composed of multiple components. Existing views on the chemical nature and the functions of each component of guinea pig complement are summarized.

Complement, also known as alexin, cytase, or addiment, is generally defined as the portion of fresh blood serum or plasma which is not increased on immunization and which, when added to certain sensitized cells, combines with these sensitized cells and, under appropriate conditions, results in their destruction or death.

Ever since its discovery, complement has continued to interest and puzzle investigators. Its theoretical importance was clearly shown by the basic experiments of Büchner, of Bordet, and of Ehrlich. Subsequent studies resulted in the practical use of complement in important diagnostic tests (complement fixation). It is especially significant in the part it plays in the actual destruction of pathogenic bacteria. Data accumulated over a number of years from several sources indicate that complement plays a major rôle in the destruction of certain microörganisms.

The bacteriologist and immunologist have made important strides in the elucidation of the biological significance of complement. Until recently, however, attempts to solve the riddle of the chemical nature and function of complement have proved difficult. The peculiar complexity and extreme perishability of complement have often discouraged the initiation or continuance of promising experiments.

Although chemists and physicists have been reluctant to enter into investigations on complement, the need of a closer coöperation between these workers and the immunologists is desirable, since the application of exact physical and chemical methods to this problem gives promise that it may be eventually solved.

It is the purpose of this review to consider complement as a chemical system composed of multiple components and to summarize, in the light of recent advances, existing views on the chemical nature and the function of each of the components of guinea pig complement.[3]

THE BIOLOGICAL SIGNIFICANCE OF COMPLEMENT

As early as 1792, John Hunter noted that blood resists putrefaction to a greater degree than other putrescible material. Later, several workers (8, 61, 98)

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[2] Present address. Army Medical School, Army Medical Center, Washington, D. C.

[3] The author's interest in this subject was initiated and sustained by close association over the course of a number of years with Dr. E. E. Ecker.

independently showed that defibrinated blood, peptone blood, and blood serum exert measurable destructive influence upon bacteria. It was further shown (61) that this bactericidal power is weakened on standing and can be destroyed by heating to 60°C. Although several theories have been advanced as to the mechanism of the destruction of bacteria by blood serum, the humoral theory of immunity as conceived by Büchner offered a theoretical basis for future work. Büchner (8) looked upon blood as containing a constituent—which he named "alexin" (protective substance)—that is responsible for the bactericidal action of blood serum. He considered alexin to be comparable to an enzyme because of its heat lability and perishability. He showed that alexin operates optimally at body temperature and is capable of destroying bacteria without the co-operation of cellular elements. Meanwhile, Bordet's experiments (2) showed that fresh serum by itself has very slight or no bactericidal action. However, fresh serum combined with heated immune serum produced powerful and rapid bactericidal effects. Thus, the mechanism of the bactericidal action of blood became clearer. Immunization of an animal produces in its blood serum relatively heat-stable protective substances (antibodies), which are specific for the antigen used in immunization. Antibodies, alone, do not destroy bacteria, but depend on the auxiliary action of another substance present in normal fresh serum, corresponding to Büchner's alexin. This substance was found to be non-specific and not increased on immunization. The discovery that immune hemolysis is in every way analogous to immune bacteriolysis led to the common use of erythrocyte–hemolysin systems in most subsequent work. Owing to the work of Ehrlich and Morgenroth (27) further great strides were made in elucidation of the mechanism of immune hemolysis. Briefly, their experiments showed the following: Red blood cells undergo hemolysis when acted upon by two serum factors, the relatively thermostable antibody (hemolysin) and the thermolabile non-specific alexin or *complement*, as Ehrlich now more properly called this substance. The antibody unites with its homologous erythrocyte in the presence or absence of complement. Complement, however, does not combine with the red cell until antibody enters into union with the cell. When this takes place, complement combines, and under appropriate conditions lysis then occurs. Continued research has added little to these fundamental initial studies, except to show that the same mechanism holds true over a wide range of antigen–antibody systems. The essential facts remain that the union of complement through the medium of the specific antibody may lead to alterations of the antigen–antibody complex; that, secondly, in other cases, a similar combination with antigen–antibody complexes may take place without any visible change occurring, the fixation of complement being shown by the disappearance of complement from the medium when a suitable test is applied. *The basis of all complement-fixation tests rests on this last fact.* From the foregoing, it is apparent that the action of complement is dependent on the nature of the substrate with which it comes into contact. There appears to be no need at the present of postulating a multiplicity of complements. Instead, emphasis should be directed to the fact that variations in the activities of complement on different antigen-antibody systems may depend either upon differences in the combining affinities of the components of complement with various antigen–antibody aggregates, or upon the relative insensitiveness of certain antigen–antibody complexes to the action of the components of complement, or finally upon differences in the nature and quality of the substrate.

Among the many functions attributed to complement are: (*1*) the hemolysis of sensitized red blood cells; (*2*) the lysis of certain sensitized bacteria (65); (*3*) the capacity to kill sensitized bacteria in the absence of bacteriolysis (61); (*4*) the opsonization of bacteria in the absence of immune serum (51); (*5*) the activation of thermostable opsonins (93); (*6*) the alteration of the rate of aggregation of antigens by their homologous antiserums (13, 39); (*7*) the alteration of the state of aggregation of antigen–antibody systems (78, 81); (*8*) and finally the property of combining with most antigen–antibody systems even in the absence of any visible manifestation (complement fixation). There is also evidence to show that complement operates in the destruction of virus by immune serum (17). Recently, it has been shown that complement plays a part in tissue sensitization (50). It has also been suggested that toxin–antitoxin aggregates bind complement *in vivo* and that by this mechanism the toxin is neutralized (55). Complement has also been associated by some workers with the coagulative processes of blood (31, 92), but recent evidence appears to invalidate this view (23, 77). There seems to be some connection between the sedimentation rate of red blood cells and the complement activity of the serum (62). Finally, although never substantiated, complement has even been associated with the biochemistry of muscle contraction (47). The criteria employed in many of the above instances as to whether complement performs the above-mentioned functions were based on the fact that the function in question is destroyed by heating the serum to 56°C. for 30 min.; and it is apparent that several of the functions attributed to complement may be due to other thermolabile constituents of serum entirely independent of complement or its components. Work with pure components of complement should clarify the biological significance of complement. In any event, there can be little doubt that complement contributes greatly to both active and passive antibacterial immunity.

THE CHEMISTRY OF THE STRUCTURE OF COMPLEMENT

Investigations into the chemistry of complement have been confronted with peculiar difficulties arising partly from the fact that complement occurs as a relatively small part of a very heterogeneous mixture (serum), and partly because of the complexity and lability of complement itself. Workers failed to appreciate the fact that complement might comprise only a small part of the serum. Indeed, it has been stated (4) only recently that "complementary power comprises all of the activities of unheated serum." Furthermore, underestimation of the extreme lability of complement when subjected to prolonged standing, changes in pH, and high temperature, and of the composite nature of complement itself led to various views as to the nature of complement.

Büchner (8) suggested that complement is an enzyme or ferment. In further attempts more clearly to define this concept of Büchner's, others have suggested that complement is a lipase (94), a protease (14), a peptidase (62), an intracellular catalyst (45), or a combination of several of these. On the other hand, it has often been inferred that complement is a simple chemical, like oleic acid (99) or similar fatty acids. It has also been proposed that complement is a lipid or a combination of lipids, soaps, and proteins (38). However, there is no evidence that the nature of complement is similar to that of any of the recognized enzymes (7). Also, subsequent studies have refuted the lipin–soap–protein complex concept (7). More commonly, complement has been considered to be a colloidal attribute of fresh serum, i.e., the activity of complement being dependent on the physicochemical state of the serum.

THE COMPONENTS OF COMPLEMENT

It is well established that guinea pig complement is composed of four functionally distinct components whose interactions result in what is commonly called complementary activity. Treatment of serum with carbon dioxide water (52) or dilute hydrochloric acid (82) or by dialysis against distilled water (9) has been shown to separate complement into two relatively thermolabile fractions. The globulin fraction or the fraction insoluble in dilute acids or in salt-free media has been designated the midpiece, and the so-called albumin fraction or the fraction soluble under the above-mentioned conditions has been termed the endpiece of complement. The activities of both endpiece and midpiece are abolished in a few minutes at 56°C. In addition, it has been shown that cobra venom (79), yeast cells (97), or an insoluble carbohydrate (67) isolated from fresh yeast inactivates or removes a relatively heat-stable fraction of complement, the third component. It has also been shown that dilute ammonia (32) and other amino compounds (68) capable of reacting with carbonyl groups destroy another thermostable component of complement, the fourth component. These two latter fractions may be distinguished from the thermolabile components by their resistance to destruction by heat up to 60°C. Claims have been made for the existence of other components, but evidence of their actual existence is lacking.

The two thermolabile components of complement owe their terminology to their supposed action rather than to their nature. The thermostable components were named according to the order of their discovery. However, functional studies raise question as to the desirability of employing the above terminology (39, 73). In addition, electrophoretic diagrams (71) (figure 1) of midpiece and endpiece prepared by the carbon dioxide method, as well as of complement deprived of its third and fourth components, indicate that the so-called globulin fraction or midpiece contains at least four distinct proteins, two of which have mobilities faster than any of those found in whole serum; while the endpiece or the so-called albumin fraction also contains at least four distinct boundaries, one of which corresponds to the gamma globulin of the normal serum. No significant difference was detected electrophoretically between normal serum and serum deprived of the fourth component of complement. Serum lacking in third component shows a disturbance of the alpha globulins. On the basis of the above findings, it has been suggested (71, 73) that the four components of complement be designated by the following symbols: C′1, midpiece; C′2, endpiece; C′3, third component; and C′4, fourth component. In the following portion of the present review the terms "midpiece" and "carbon dioxide-insoluble fraction" are used interchangeably, as are the terms "endpiece" and "carbon dioxide-soluble fraction," and the symbols C′1 and C′2 represent the midpiece and endpiece *components per se.* The third and fourth components are used interchangeably with the symbols C′3 and C′4, respectively.

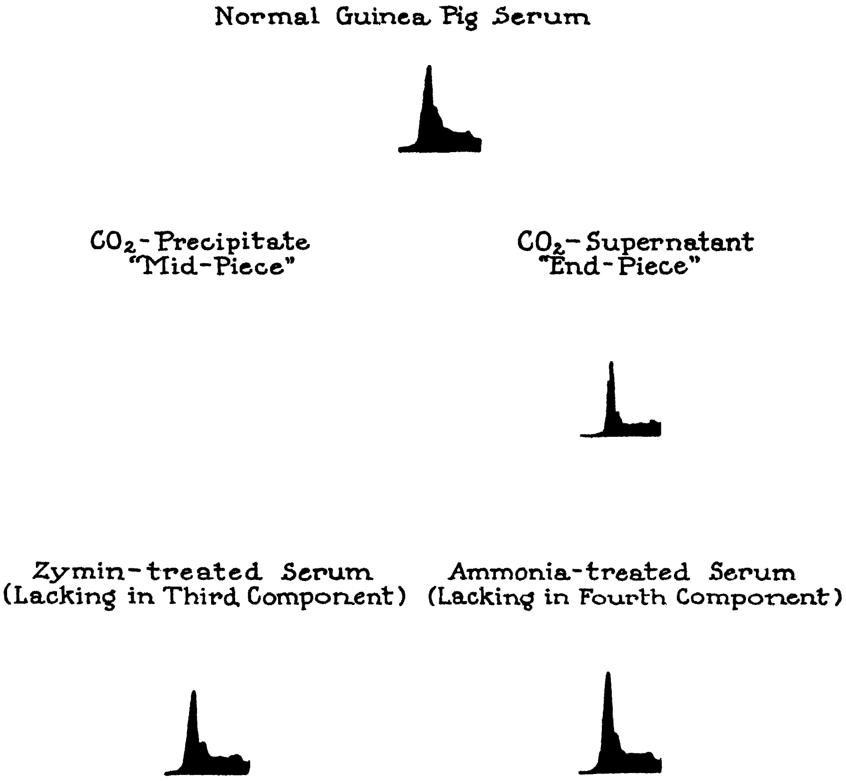

FIG. 1. Electrophoretic schlieren patterns of normal guinea pig serum and guinea pig serum treated with various reagents which separate or destroy the components of complement. Descending boundaries of the proteins in phosphate buffer of pH 7.7 and ionic strength 0.2. Scanning exposures made after electrolysis for 2½ hr. Pillemer and Ecker (71).

The recent work of Hegedüs and Greiner (35) should be mentioned. These authors found that the differences in the hemolysis of sensitized sheep red cells by the complements from various species of animals are due to variations in the content or activities of the different complement components in each serum.

These differences were found to be constant and characteristic of each species. They claim that the complement titer of serum is determined by the component present in the lowest titer. These components are midpiece for the guinea pig, endpiece for the human and rabbit, and C′4 for the hog. Guinea pig complement contains a fuller quota of all components than other serums, which accounts for its powerful complementary action against sensitized sheep cells. Hegedüs and Greiner further showed that cow, horse, sheep, and squirrel serums do not hemolyze sensitized sheep cells because of the absence of endpiece activity in all of these. It is evident from the results of Hegedüs and Greiner that great caution must be observed in interpreting data derived from studies on the complement activities of one species to fit the activities of the complements of all other species. However, confirmation of the Hegedüs and Greiner findings with the use of *purified* components of complement is desirable. In any case, the value of their results lies in the exposition that complement activity is determined by the activity of the weakest component present and that one component of complement cannot replace another.

It is apparent that complement function is associated with the protein consituents of blood serum, and is distributed over several protein fractions, which interact with one another and not merely in the manner of summation. Most attempts to separate complement from whole serum have yielded results too indefinite to allow the characterization either of complement or of any of its components as functionally distinct entities. Indeed, Browning (7) in summarizing the literature on complement up to 1931 stated that, "at present it is impossible to determine whether complement is of compound nature, as is believed to be the case for enzymes, or whether it may represent a physicochemical state of a mixture of proteins, lipins and other constituents of the serum." However, some advance in the purification and characterization of the components has been made, and for greater ease in presentation and for the sake of clarity, the chemistry of the existing knowledge of each component of complement will be reviewed and discussed.

THE CHEMISTRY OF MIDPIECE

The globulins, which separate out when a complement-containing guinea pig serum is treated with either carbonic acid or weak hydrochloric acid or by dialysis against distilled water, contain all of C′1, a major portion of C′3, and a small part of C′4 of complement. As prepared by carbonic acid precipitation, this fraction, judged electrophoretically (71), consists of at least four serum proteins, one of which has an electrophoretic mobility of 2.9×10^{-5} in phosphate buffer of pH 7.7 and an ionic strength of 0.20. Eagle (19a) has recently investigated the midpiece of complement in the ultracentrifuge and found that this fraction of complement sediments faster than the other components of complement. The isoelectric point of midpiece has been reported variously between pH 5 and 6. It is non-dialyzable through cellophane against distilled water, hypertonic salt solution, or hypotonic salt solution (25). A dilute solution of midpiece in 0.9 per cent sodium chloride loses its activity in a few hours at room temperature or at ice-box temperature (5°C.), in 30 min. at 54°C., and almost instantaneously at temperatures above 60°C. (25). It has been reported (57) that after midpiece combines with antigen–antibody complexes, its further activity is then unaffected by heating at 56°C. for 30 min. While midpiece is extremely unstable in 0.9 per cent sodium chloride, it can be kept for days suspended in distilled water or dissolved in hypertonic salt solution at a pH between 5.8 and 6.2 (25). It is partially inactivated at a pH of 8.8 or 4.2, and completely inactivated at pH 9.5 or over, or pH 4.0 or under, being more stable in acid than in alkaline solution (70). Midpiece is inactivated by shaking, by ultraviolet light (33, 84), and by organic solvents (66), e.g., ether, alcohols, benzene, chloroform, and acetone. Its activity is inhibited or destroyed by colloids possessing strong acidic groups (23), such as cellulose sulfuric acid, crystalline heparin, hyaluronic acid, and chondroitinsulfuric acid, and also by protamine sulfate and diethylamine. Midpiece is susceptible to adsorption by inorganic adsorbents such as lead phosphate and titanium dioxide (24), by sensitized and unsensitized cells (63), and even by filtration through a Berkefeld filter (87). Summarizing, midpiece has the character of a globulin, and is extremely sensitive to physical or chemical conditions different from those encountered in its natural environment.

Attempts have been made to purify midpiece. Browning and Mackie (6) and Parsons (64) were unable definitely to establish midpiece in any distinct serum protein fraction. Tokunaga (90) even casts doubt on the individuality of midpiece. However, all of the above-named authors agreed on the globulin nature of midpiece. Ferranti (30) later characterized midpiece as a subfraction of the acid globulins and as having a low isoelectric point. Doladilhe (16) also established midpiece as being an acid globulin, insoluble in distilled water or carbonic acid at low salt concentrations, but soluble in carbonic acid in the presence of 0.9 per cent sodium chloride. However, none of the above preparations was fully characterized and therefore their exact identities are unknown.

THE PURIFICATION AND CHARACTERIZATION OF GUINEA PIG C′1

The separation of C′1 from guinea pig serum has been achieved (72) by adherence to exact physicochemical manipulations with rigidly controlled conditions of temperature, hydrogen-ion concentration, and ionic strength. The procedure in brief consisted of the precipitation of the active principle by 1.4 *M* ammonium sulfate at low temperatures, followed by isoelectric precipitations and extractions. Final purification was aided by the observation that, whereas the active principle C′1 was quantitatively precipitated at an ionic strength of 0.02 at pH 5.2, a fair proportion of other euglobulins as well as pseudoglobulins remained in solution, thus leading to a high degree of purification of C′1. Fully 95 per cent of the euglobulin separated by the above procedures showed an electrophoretic mobility of 2.9×10^{-5} when measured in phosphate buffers of ionic strength of 0.2 at pH 7.7, and all of the molecules sedimented with the same velocity in the ultracentrifuge, calculated to be 6.4×10^{-13} Svedberg units, when measured in 0.2 *M* potassium chloride. The final yield of this material from

1070 ml. of serum was 400 mg. or 0.6 per cent of the total serum proteins. Stability studies on the purified C′1 revealed that while it was unstable at neutral pH, its activity remained intact at pH of 5.4 to 6.0. No C′1 activity was observed at protein concentrations exceeding 0.02 per cent, while full activity was observed at protein concentrations between 0.002 and 0.02 per cent. The presence of excess lipoidal material also interferes with the activity of C′1, which may account for the failure of workers to obtain midpiece activity in the proteins precipitated at one-third saturation ammonium sulfate. The properties of C′1 are summarized in table 1.

TABLE 1[*]

Properties of C′1

PROPERTIES	C′1
Mobility in phosphate buffer, at pH 7.7, 0.2 ionic strength	2.9×10^{-5}
Sedimentation constant, $s_{20^{\circ},w}^{1\%}$	6.4×10^{-13}
Protein nitrogen, per cent	16.3
Carbohydrate, per cent	2.7
Phosphorus, per cent	0.1
Optical rotation, $[\alpha]_{D}^{25^{\circ}}$	−28.7
Apparent isoelectric point	5.2–5.4
Fraction of total serum protein, per cent	0.6
Heat stability of complement, activity (destroyed in 30 min. at tabulated temperature), °C.	50

[*] Reference 72.

THE CHEMISTRY OF ENDPIECE

The fractions of guinea pig serum which remain in solution when the serum is treated with carbonic acid or weak hydrochloric acid or by dialysis against distilled water, contain all of C′2, a major portion of C′4, and a small part of C′3. In carbonic acid precipitation, this soluble fraction contains at least four protein fractions as observed electrophoretically (71), two of which are albumin and gamma globulin. Eagle (19a) has attempted to characterize endpiece in the ultracentrifuge and his studies show that endpiece sediments with the same velocity as the serum albumins. Endpiece is non-dialyzable against distilled water and salt solutions (25). In contrast to midpiece it is relatively stable on standing, maintaining its activity for several days at ice-box temperature (3–5°C.). However, its activity is abolished in 30 min. at 54°C. and instantaneously at temperatures above 60°C. The presence or absence of salt appears to make little or no difference in its stability as long as the pH is maintained between 6.2 and 7. It is more stable in alkaline solutions than in acid solutions (70). Thus, whereas a pH of 10 or over is needed to inactivate endpiece totally, at a pH of 5.8 or under its activity rapidly disappears. Endpiece is inactivated by shaking, by proteolytic enzymes, and by organic solvents (66). Its activity is destroyed by ultraviolet rays (33, 84), although it is more resistant in this respect than midpiece and in the dry state is only slightly affected by ultraviolet light. Endpiece is readily adsorbed when passed through a Berkefeld filter (87). Like midpiece, it is inactivated by treatment with highly acidic colloids and extremely basic proteins or colloids (23).

THE PURIFICATION AND CHARACTERIZATION OF GUINEA PIG C′2

Endpiece has been usually associated with the albumins or psueodoglobulins of serum (63). Ferranti offered the first evidence that it is not identical with the serum albumins, but that it is associated with the "albuminoids" (28). He claimed to have separated the active endpiece principle by adsorption with fibrinogen (29). However, because Ferranti did not characterize his preparations, their true identify remains obscure.

Recently (72), a mucoeuglobulin has been isolated from guinea pig serum which exhibits both C′2 and C′4 activity. This mucoeuglobulin, which separated after the dialysis against conductivity water of the serum proteins soluble at a concentration of 2.0 *M* but insoluble at a concentration of 2.2 *M* ammonium sulfate, has mainly an electrophoretic mobility of 4.2×10^{-5} in a phosphate buffer of pH 7.7 and 0.2 ionic strength. Ultracentrifugal analysis of this fraction revealed several boundaries. The sedimentation constants observed—17, 6.3, and 3.8×10^{-13} units (in amounts of 5, 35, and 60 per cent, respectively)—are close to those reported for purified alpha globulins from other species. A study to determine if the fraction containing these components of complement represents a single component in the ultracentrifuge, several independent components, or several components in equilibrium with each other is definitely indicated.

As stated above, the mucoeuglobulin possesses both C′2 and C′4 activity. This was not the first indication of the close relationship of these two fractions of complement. Whitehead, Gordon, and Wormall (96) suggested that these two components might be closely associated, since they had noticed that the fraction of serum soluble in carbonic acid generally contains these two components. Further studies by others (68) substantiated this hypothesis, and extended the view that the two components are a carbohydrate-protein complex. For a fuller understanding of the nature of C′2, the chemistry of C′4 should best be elaborated and the nature of the two components discussed simultaneously.

THE CHEMISTRY OF C′4

Complementary activity can be removed from blood serum by appropriate concentrations of ammonia in such a manner that the activity can be regenerated by the addition of serum lacking in either C′1, C′2, or C′3. Gordon, Whitehead, and Wormall (32), who first observed this fact, found that the ammonia effect is not due simply to alkalinity, but that it is a specific reaction involving a relatively thermostable fraction of complement. This component is characterized as being non-identical with the third component, as being non-dialyzable, and as being capable of destruction by dilute acids and alkalies at 37°C. These authors designated this fraction of complement as the fourth component. They also stated that, of the other amino compounds, primary methylamine and ethylamine behave like ammonia in inhibiting the fourth component, while glycine, alanine, and urea do not. Others have claimed that viper venoms inactivate a similar factor (63). Attempts have also been made to associate the fourth component with lipids and bound calcium (63), but recent evidence appears to invalidate the view that lipids and calcium play a rôle in the structure of fourth component (69). In fact, it has been shown that the extraction of lipids from serum by numerous organic solvents does not specifically inactivate C′4 (66), and the weight of experimental evidence indicates that calcium is not involved in the immediate labile reactions of C′4 nor is it a part of its internal structure. Since inactivation of C′4 (34) is not associated with the protein constituents of serum or with any interferences with the phosphorus partition or with the lipids or calcium of serum, the hypothesis (68) has been offered that the ammonia inactivation of the fourth component is due to the conversion of the active carbonyl groups of the component to some less active structure. This hypothesis was tested by extending the work of Gordon and his coworkers to include various amino compounds of two general classes: namely, those which are known to react readily with aldehydes and those which do not. The results obtained are summarized in table 2, which reveals that only amino compounds capable of reacting with carbonyl groups specifically inactivate C′4. Simple alkalinity of the amines is not the cause of the inactivating property. In water, the effective compounds dissociate to form bases of moderate strength, but it is readily seen that many of the inactive compounds dissociate in the same manner. In fact, the dissociation constant for tetramethylammonium hydroxide or triethylamine is greater than that of ammonia or phenylhydrazine. The —NH_2 group is necessary for inactivation of the fourth component. Hydrazine, with two —NH_2 groups, requires only one-half the concentration of ammonia to inactivate C′4. The type of substituent group replacing a hydrogen atom of ammonia to produce the amino compound has a pronounced influence on the

TABLE 2*

Properties of a mucoeuglobulin possessing C′2 and C′4 activity

PROPERTIES	C′2 AND C′4
Mobility in phosphate buffer, at pH 7.7, 0.2 ionic strength	4.2×10^{-5}
Protein nitrogen, per cent	14.2
Carbohydrate, per cent	10.3
Phosphorus, per cent	0.1
Optical rotation, $[\alpha]_D^{23°}$	−192.5
Apparent isoelectric point	6.3–6.4
Fraction of total serum protein, per cent	0.18
Heat stability of complement, activity (destroyed in 30 min. at tabulated temperature), °C.	50†, 66‡

* Reference 72.

† For endpiece activity.

‡ For fourth component activity.

capacity of the compound to inactivate the fourth component. A positive substituent (simple alkyl), as in methylamine, continues to act as does ammonia. A negative substituent (phenyl group) diminishes the amino effect on C'4. Polar groups which potentially lend acidic or redox properties to the amino compounds completely abolish the effect on the fourth component. This is seen in such compounds as the carbazides, urea, glycine, and hydroxylamine. Amino compounds which have been treated previously with aldehydes do not inactivate the fourth component. The fourth component of complement cannot be reactivated by the addition of aldehydes to serums treated with amino compounds. This indicates that a firm union exists between the amino compounds and the reactive group of the fourth component. Further, the union is sufficiently stable to resist dialysis against 0.9 per cent sodium chloride. These results suggest that the amino compounds act upon a reactive carbonyl group of serum which is most likely associated with a glucoprotein. Further studies have shown that the fourth component is relatively stable in alkaline solutions, but unstable in slightly acid solutions. Its pH range of stability is of the same order as that of C'2 (70). C'4 is relatively stable on standing; at 1°C. its activity remains unimpaired for several days. It is non-dialyzable and retains its activity after heating at 56°C. for 30 min., but is readily inactivated at temperatures above 60°C., being inactivated in a few minutes at 65°C. (21). C'4 is quite resistant to non-specific adsorption. Indeed, twelve consecutive filtrations through a Berkefeld filter are required to remove this component from serum (87). C'4 is far more resistant to ultraviolet light than are the thermolabile components of complement (33, 84).

The above-mentioned properties of C'4 may explain past failures to purify complement by fractionation with ammonium sulfate, because unless care is taken to maintain slightly acid pH and low temperature during purification, inactivation of C'4 readily occurs. In this respect, Tokunaga (89) has shown that ammonium sulfate inactivates complement, the rate of inactivation increasing on raising the temperature or on dilution of the serum. He further found that a large excess of ammonium sulfate fails to inactivate complement. Apparently, the acidity of the excess ammonium sulfate is sufficient to suppress the ionization of reactive amino groups.

As stated above, C'2 and C'4 were found to be present in the same mucoeuglobulin of guinea pig serum. Treatment of this protein at 50°C. for 30 min. removed all of its endpiece activity, but did not inhibit C'4. This euglobulin then retained two functions, one by virtue of a relatively heat-labile, and the other by virtue of a relatively heat-stable component. Its carbohydrate content was 10.3 per cent and it reduced Schiff's reagent. These findings are not inconsistent with the hypothesis that C'4 is a carbohydrate with reactive carbonyl groups and that it is associated with C'2 as a complex. The heterogeneity of the sedimentation patterns of the mucoeuglobulin makes it advisable, however, to postpone a definite assumption as to its exact nature until more detailed study of this protein is undertaken. The properties of the mucoeuglobulin are given in table 3. It is noted that the yield of this protein from 1070 ml. of serum was

120 mg., or less than 0.2 per cent of the total serum proteins. The mucoeuglobulin is characterized by an extremely high levorotatory optical activity and by low phosphorus content. It exhibits full activity at dilutions of 0.01 per cent and shows no inhibitory action on the addition of excess quantities, as was found for C′1.

TABLE 3[a]

The effect of amino compounds on the fourth component of complement

SUBSTITUENT TYPE	REAGENT	FORMULA	MINIMAL MOLARITY	MAXIMAL MOLARITY	pH	INACTIVATION OF FOURTH COMPONENT
Positive........	Ammonia	HNH_2	0.16		8.5–10	+
	Methylamine	CH_3NH_2	0.12	0.24	7.4– 8.0	+
	Dimethylamine	$(CH_3)_2NH$		0.72	7.0–10	–
	Trimethylamine	$(CH_3)_3NH$		0.72	7.0–10	–
	Tetramethylammonium hydroxide	$(CH_3)_4NOH$		0.96	7.0–10	–
	Ethylamine	$CH_3CH_2NH_2$	0.12	0.24	8.0– 9.0	+
	Diethylamine	$(CH_3CH_2)_2NH$		0.72	7.0–10	–
	Triethylamine	$(CH_3CH_2)_3N$		0.72	7.0–10	–
	Hydrazine	H_2NNH_2	0.08		7.2– 8.0	++
Negative........	Phenylhydrazine	$C_6H_5NHNH_2$	0.24	0.36	7.0– 7.4	+
	Aniline	$C_6H_5NH_2$		0.64	7.0–10	–
Polar...........	Urea	NH_2CONH_2		0.95	7.0–10	–
	Acetamide	CH_3CONH_2				
	Glycine	$HOOCCH_2NH_2$		0.96	7.0–10	–
	Semicarbazide	$H_2NCONHNH_2$		0.72	6.0–10	–
	Thiosemicarbazide	$H_2NCSNHNH_2$		0.72	7.0–10	–
	Hydroxylamine	$HONH_2$		0.72	6.0–10	–
Blocked polar...	*O*-Methylhydroxylamine	CH_3ONH_2	0.16	0.24	8.5– 8.5	+
Indifferent......	Methenamine	$(CH_2)_6N$		0.96	7.0–10	–

[a] Reference 68.

THE CHEMISTRY OF C′3

Although the inactivation of complement by yeast cells was described by von Dungern as early as 1900 (97), the nature of the phenomenon remained obscure until Coca (10) established that the inactivation by yeast is due to the removal or destruction of a relatively heat-resistant portion of complement, and not to the introduction of inhibiting substances. Whitehead, Gordon, and Wormall (96), employing a yeast powder, found that the third component combines either physically or chemically with the yeast powder. It has also been found that cobra venom (79) and weak solutions of formaldehyde (11) inactivate the third component. Certain other agents which inactivate complement appear, in part, to exert their effect on C′3, i.e., bacterial suspensions (79), hexoxidases (20), and strong reducing agents (69). The divergent qualities of these inactivating agents make it difficult to draw conclusions as to the chemical structure of C′3. An insoluble fraction (67) from fresh yeast also adsorbs C′3 from fresh serum. This insoluble material is composed of 94 per cent carbohydrate and is insoluble in hot water, salt solutions, and organic solvents. The yield from fresh yeast is about 2 per cent. The insoluble carbohydrate inactivates the third component specifically in an amount only one twenty-fifth of the required amount of fresh yeast. None of the soluble fractions from yeast inactivated C′3. Since the anticomplementary factor in fresh yeast is undoubtedly this insoluble fraction, the inactivation of C′3 appears to be due to the adsorption of this relatively heat-stable component from serum. Recently, the amount of nitrogen removed from serum by the insoluble carbohydrate has been measured (26). It was found that the removal of the third component from 1 ml. of guinea pig serum is accompanied by the uptake by the insoluble carbohydrate of about 0.02 to 0.03 mg. of nitrogen. Little or no phosphorus is adsorbed. Elution studies on the adsorbed material are in progress. The results of such studies should do much to clarify the constitution of this hitherto unidentified component. Attempts to purify C′3 by the classical methods of ammonium sulfate fractionation have been unsuccessful. In these experiments, third component is present in small quantities in nearly every fraction of serum, especially in the euglobulins.

C′3 is resistant to inactivation at a temperature of 56°C., but is destroyed in 30 min. time at 62°C. (21). C′3 is the first component of complement to disappear on standing at room temperature. Its stability to changes in hydrogen-ion concentration is of the same order as that of C′1, since it is relatively stable in weak acid solutions and very unstable in weak alkaline solutions. It is non-dialyzable against distilled water, hypertonic or hypotonic solutions, or weak acid solutions.

Hypertonic salt solutions exert a protective action on C′3, in that C′3 becomes more resistant to inactivation on standing, and in that it cannot be removed from guinea pig serum by yeast, zymin, or the insoluble carbohydrate from yeast in the presence of 5 per cent or more of sodium chloride. The inactivation of complement on dilution with distilled water appears to be due to the destruction of C′3 (63). On the other hand, dilution of serum with saline is said to protect the third component from heat inactivation (7).

THE CHEMISTRY OF COMPLEMENT FUNCTION

General considerations

It was originally supposed by Ehrlich that the nature of complement action is similar to the mechanism by which living protoplasm obtains its nutrition; when complement combines with the sensitized cell, it was thought that a catalytic digestion follows. Others have also viewed complement as a catalyst or enzyme. Scheller (83), influenced by Pfeiffer's opinion as to the mechanism of bacteriolysis, put forth the view that complement acts as a catalyst to the antibody, the latter then exerting an enzymic action. Hill and Parker (45) state that complement, during the interval between its combination and its entrance into the cell, acts as a catalyst and allows the release of hemoglobin by the associated antibody. On the other hand, McKendrick (56) concluded that the action of complement is lytic *per se*, the antibody acting as a catalyst to complement after fixation. Ponder (76) questions the interpretations of Hill and Parker and of McKendrick and offers experimental evidence to disprove their hypothesis. Furthermore, complement has not been identified with serum proteases and lipases, and there is insufficient evidence that complement produces enzymic decomposition such as is brought about by recognized ferments. In further attempts to define complement chemically, it has been suggested that complement action is analogous to the action of soaps. Noguchi showed that the hemolytic organ extracts were soap-like in nature (60), and attempted to associate this observation with complement function. Subsequent studies have shown that the hemolytic action of soaps is not destroyed by heating and that they operate just as well on unsensitized as on sensitized cells.

The observation that complement is apparently consumed in the process of hemolysis or bacteriolysis led workers to investigate the nature of this phenomenon. Liefmann and Cohn (53) believe that the disappearance of complement is due to several factors: first, to the fixation of complement by the products of the red blood cell after hemolysis; second, to the dilution of complement, thereby increasing its instability; third, to the weakening of complement because of prolonged exposure to dilute solution at 37°C. Eagle and Brewer (19) and Ponder (76), however, disagree with Liefmann and Cohn in that they believe that the disappearance of complement is due to the adsorption of complement by the sensitized cell previous to lysis. The general belief is at present in agreement with the views of Eagle and Ponder.

Konikov (48, 49) has reported some interesting observations on the nature of the mode of action of complement and hemolysin that bear reporting in some detail. Konikov believes that the combination of the red blood cell with antisheep red blood cell rabbit serum follows Freundlich's equation of physical adsorption only when there is an excess of antiserum. The exponent of the isotherm is between 0.22 and 0.35. In low concentration of hemolysin, a strictly chemical reaction between the erythrocyte and antiserum predominates. Konikov further showed that the combination of immune serum and red blood cell is dependent on pH, the optimal hydrogen-ion concentration lying between pH 6.0 and pH 6.7. Furthermore, this combination is dependent on the salt concentration, and the nature of the salt is not as significant as the concentration employed. The active concentrations of all salts are approximately equivalent. Konikov further assumes that an ionic reaction occurs in the process of sensitization with the formation of a complex combination of salt, red cell, and antiserum. Continuing, he states that the hemolysis of sensitized cells by complement occurs only in the presence of salts whose effective concentrations are directly dependent on their equivalence. He concludes that the combination between complement and red cell is purely chemical and that osmotic pressure phenomena do not play a rôle in this sort of hemolysis. This is in good agreement with the fact that stroma is not destroyed in complement hemolysis and that when lysis has been effected by lytic serum the stroma remains practically unaltered in different concentrations of salt. Apparently the hemolysis of the cell by complement has so increased the red cell permeability that simple osmotic phenomena no longer play a significant rôle. To return to Konikov's experiments, he further found that pH 7 is optimal for complement action. He explains the relationship between hemolysis, hydrogen-ion concentration, and the nature and concentration of the employed salt on the assumption that complement concentrates on the surface of the cell, where it combines to form a layer of protein having an isoelectric point of 4.7. This creates between the cell contents and the surrounding complement layer, in accordance with Donnan's law, a potential difference and an electrical field. Water is then driven electroösmotically through the stroma pores of the red cell along the lines of force; this causes a drop in the osmotic pressure within the red cell and then hemolysis occurs.

Eagle (18, 19) has pointed out that the physical constants of complement fixation,—namely, temperature coefficient, velocity, and quantitative relationships between reactants,—are those commonly associated with adsorptive processes. Eagle also mentioned the possibility that the enormous avidity of antigen–antibody aggregates for complement may be due to a specific chemical affinity. This author has also reported interesting observations on the mechanism of immune hemolysis which demonstrate that sensitization of the red cell confers upon it the property of adsorbing complement, and that the degree of sensitization determines the amount of complement fixed. Eagle found that variations in the electrolyte and hydrogen-ion concentration markedly influence the fixation of complement and subsequent hemolysis. On the basis of his findings Eagle states, "if this mobilization of complement is the sole function of immune serum (and there is as yet no reason to assume any other) then the accepted terminology, in which amboceptor, immune body and hemolysin are used synonymously, is erroneous. The immune body would function only as an 'amboceptor' mobilizing the effective hemolysin, complement, upon the surface of the cell." Recent work discussed below has served to substantiate Eagle's views.

Continuing along similar lines, Brown and Broom (5) have reported some interesting experiments on the possible mode of action of complement. The authors noted that the negative charge normally carried by bacteria and red blood cells is reduced considerably by the action of specific immune serum in the presence of electrolytes, and that the negative charge on the red cell is reduced in proportion to the amount of antiserum used to sensitize the cell. In the absence of electrolytes they found no reduction in the cell charge, even though the cell had been heavily sensitized. Extending their experiments, they showed that complement behaves as though it is negatively charged at neutral pH, and that the effective action of complement is dependent on the valency of the salt, provided, of course, that the salt itself has no deleterious effect on the complement. The electrolyte apparently lowers the charge of the red cell in the presence of immune serum, and when the charge is reduced to the required potential the negatively charged complement is fixed. This hypothesis would explain the findings of Sachs and Teruuchi (81) and of others that the absence of salts inhibits hemolysis by complement, and would also explain the inhibition of complement action by polyvalent anions, since the work of Loeb (54) demonstrates that the negative charge of colloids is first increased when acted upon by polyvalent anions and is only decreased in high concentration of salt. It should be pointed out that Brown and Broom make no claim that the charge of the antigen–antibody complex is the sole factor in fixation and hemolysis, but maintain that it is an essential preliminary process. Hambleton's (36) results also indicate that the fixation of complement is only a secondary effect due to the surface properties of suitably modified antigens and not to a specific chemical affinity of the antigen for complement.

While it is agreed that the electrical state of the reactants,—complement, antigen, and antibody,—is an important factor in the fixation of complement, the composite nature of complement and the multiple functions of its components do not allow an elementary explanation such as simple adsorption for this action. On an adsorption basis, alone, it would be difficult to explain the selective fixation of C′1 by immune compounds while other serum euglobulins of similar isoelectric points and net charges remain unadsorbed. Furthermore, the attraction of C′3 to non-specific agents such as inorganic adsorbents and unsensitized bacteria, and not to immune aggregates, and the avidity of C′4 and C′2 for antigen–antibody compounds and not for non-specific adsorbents cannot be explained by simple adsorptive phenomena. While it is the general belief that electrical phenomena and other physical factors enter into the fixation of complement by immune aggregates, recent evidence also indicates that a certain degree of specificity accompanies such manifestations, and that such specificity involves chemical phenomena.

In the foregoing considerations, complement has been treated as a single entity, the final test for its presence being the occurrence of hemolytic or bacteriolytic action. However, as shown in this review, complement is composed of several components, the absence of any one of which leads to the inactivity of the total complement complex. Consequently, it is obvious that the fixation of complement may depend on the removal or inactivation of only one or more of the components of complement, and that hemolysis must be the result of the interactions of all of the components of complement. As will be seen later, this is true, and the varied results obtained by different workers have been due for the most part to their reluctance to accept a composite nature of complement. Furthermore, failure to distinguish between the primary stage of complement action (fixation) and the secondary stage (lysis, etc.) has also greatly contributed to many varied views.

Recently, there has been an advance in the knowledge of the fixation of the components of complement. Of particular significance are (*1*) the identification of the combining components of complement (73), (*2*) the investigations on the physical and chemical factors governing the fixation of the components of complement (73), and (3) the development of methods for the quantitative estimation of the combining components (39). In this section, an attempt is made to summarize especially these developments.

THE IDENTITY OF THE COMBINING COMPONENTS OF COMPLEMENT

Although most investigators have generally accepted the belief that midpiece is the combining component of complement, the adequacy of this belief has often been questioned. Brin (3) holds that the endpiece of complement is the combining component of complement. Others (12, 85, 86) assert that both midpiece and endpiece combine with antigen–antibody compounds. Still others (1, 15, 58, 91) have shown that C′4 is involved in complement fixation. The work of Nathan (59) and of others (88, 95) clearly shows that C′3 does not combine with sensitized cellular antigens such as red cells. There are several reasons for these varied views. First, with the exception of a few recent studies, investigations on the rôle of the complement components in immune fixation were performed before the discovery of the fourth component. Second, much of the past work was qualitative in nature with little consideration of the chemical and physical factors which affect the combination of the complement components with antigen–antibody aggregates. Third, the results obtained under one set of experimental conditions were frequently interpreted to fit all other experimental conditions. Fourth, the methods for the preparation and identification of the components of complement employed in the fixation studies were usually not uniform.

Deissler (15) first pointed out that C′4 combines with immune aggregates. His results show that sensitized sheep cells fix the fourth component of complement and that the fixation of C′4 appears to be a prerequisite for the fixation of midpiece or endpiece. C′4 is only slightly or not at all adsorbed from heat-inactivated serum. Other findings are in agreement with Deissler's. Misawa (58) and his associates have also shown that in the Wassermann reaction, while C′4 as well as endpiece and midpiece are fixed by strongly positive serums, C′4 does not always combine with the aggregates of weakly positive serums. On the other hand, these authors found that the aggregates of low-titer rabbit antiserums fix C′4 with little or no fixation of C′3, endpiece, and midpiece, and that the aggregates of high-titer rabbit antiserums fix all of the components. It appears from the results of these studies that the nature of the antigen or antibody, as well as the titer of the antiserum, influence both quantitative and qualitative fixation of the complement components. It has also been claimed (46) that only those guinea pig proteins which are soluble in one-third saturation but insoluble in one-half saturation of ammonium sulfate are fixed by antigen–antibody complexes.

The influence of physicochemical conditions on the fixation of the complement components have been recently studied (73). It was found that the amount of each component which combines with specific immune aggregates depends upon a number of factors, including the age of the complement, the concentrations of antigens, antibodies, and complement, the hydrogen-ion concentration, the electrolyte concentrations, and the time and temperature of incubation for fixation. In more detail, it was shown that when serum had stood in the ice chest overnight and had lost 50 per cent of its complementary activity, C′4 became more resistant to fixation, more C′2 was fixed, and less C′1 combined. The combination of C′3 was unaffected. It was further shown that C′4 is fixed during the first 5 min. of incubation if a sufficiently high titer antiserum is employed. Under similar conditions, maximum fixation of C′1 occurs after 40 min. of incubation. The effect of temperature on the fixation of the components is striking, in that at temperatures of 37°C. C′4 is more resistant to fixation. These authors (73) also showed that, whereas complementary activity is removed over an an extremely wide pH range, there is, however, marked variation in the fixation of the individual components. At a pH below 7, less fixation of C′4 and C′1 occurs than at pH 7, while at a pH above 7.0 complete fixation of C′4 occurs, together with an increased fixation of C′1. Studies of the effect of salt concentration on the fixation of the complement components revealed that the combining components are fixed incompletely in slightly hypertonic solutions, while in hypotonic solutions little or no variation in the addition of the combining components occurs. It has been further demonstrated that dilution of serum previous to fixation results in less fixation of C′4 with an increase in the combination of C′1 and C′2. The concentrations of antigen, antibody, and complement employed in fixation experiments were shown to have a marked influence on the union of the combining components with immune aggregates. In great excess of antigen or antibody, the fixation of the combining components is greatly inhibited; this phenomenon is most marked in extreme antigen excess. Also, very dilute solutions of both antigen and antibody fix complement, especially C′4, incompletely. From the foregoing observations, the conclusions were drawn that *the fixation of each individual component of complement is both influenced by and dependent on definite physicochemical conditions.* This is not entirely unexpected when the marked variations in the chemical character of the components of complement are considered.

Adherence to the immunochemical conditions of fixation described above has resulted in the exact identification (73) of the combining components of complement and in the determination of the amounts of their activity removed by combination with immune aggregates. These studies revealed that C′4 must be considered a definite combining component of complement, since it is invariably inactivated or adsorbed by immune aggregates. C′2, which is usually fixed along with C′4, must therefore also be considered a combining component. Mid-piece, which contains C′1 and which is generally stated to be the single combining component of complement, is adsorbed by immune aggregates in varying amounts depending on the experimental conditions employed. C′3 is only partially or not at all fixed by soluble antigens in the presence of their specific antiserums, or is not fixed by sensitized red blood cells. No inactivation or adsorption of C′4 occurs when serum which has been heated at 56°C. for 30 min. is added to specific aggregates, nor is C′4 adsorbed from endpiece. Inactivation of C′4 by ammonia or hydrazine or the removal of C′3 by the insoluble carbohydrate from yeast does not markedly influence the fixation of the other components of complement. Studies with various types of antigen–antibody aggregates show that the nature and molecular size of the antigen do not influence the qualitative picture of fixation of the complement components.

From the foregoing evidence, it is apparent that C′4, C′2, and C′1 should be considered combining components of complement. Furthermore, there are certain differences between the fixation of the components to specific aggregates and the union of these components to non-specific agents. For example, in non-specific adsorption both on inorganic adsorbents and on untreated bacteria, no fixation of C′4 and C′2 occurs, while C′1 and C′3 are adsorbed. On the other hand, it is now definitely established that immune aggregates combine with C′4, C′2, and C′1, while little or no fixation of C′3 occurs. It appears, therefore, that C′4 and C′2 are distinctly and immediately involved in specific immune fixation. The above facts may account for the observation, as yet little understood, that a very small amount of specific immune aggregate combines with a relatively large amount of complement, while a relatively large amount of a non-specific agent is required for the adsorption of only a small amount of complement. This difference in the combining activities of the two types of adsorbents may be due to the differential affinities of the specific immune compounds and the non-specific adsorbents for C′4. If this be so, then investigations with this component may do much to increase the sensitivity and specificity of the various diagnostic complement-fixation tests.

Meanwhile, the evidence derived from recent data appears to warrant the conclusion that "when complement exerts its activity in hemolytic, bacteriolytic, or bactericidal reactions, C′4–C′2 and varying amounts of C′1 must first combine (fix) with the antigen–antibody compound in question; and that any secondary reaction is dependent both upon the adjunctive action of the unbound C′3 and upon the nature of the substrate employed" (73).

Although it is now generally agreed that complement or, more strictly speaking, its combining components, combine with certain antigen–antibody precipitates, the actual addition of the combining components in weight units has not been measured until recently. Haurowitz (37), who could not detect any increase in the weight of the specific precipitates of ovalbumin or of azoproteins, when complement was added to them, nor any change in the content of antigen in the precipitates, assumed from his data that in complement fixation only a small group of the complement complex is bound to the antigen–antibody compounds.

On the other hand, Heidelberger (39), employing quantitative methods conforming to the criteria of analytical chemistry, was able to measure in milligrams of nitrogen a difference between the amounts of specifically precipitated nitrogen found in the presence of untreated guinea pig serum and in the presence of guinea pig serum which had been inactivated at 56°C. for 30 to 60 min. In a series of well-planned experiments he showed that this additive nitrogen is intimately associated with complement and is not due to non-specific nitrogenous components of serum. He further stated that midpiece of complement added nitrogen to specific precipitates, while endpiece behaved like heat-inactivated serum and did not add nitrogen. On the basis of his findings and on the general belief that midpiece is the combining component of complement, Heidelberger provisionally designated the additive nitrogen as C′1 nitrogen. Later, Heidelberger (44) and others (75) showed that other components of complement contribute nitrogen to specific precipitates.

Heidelberger, Silva, and Mayer (41) further showed that the uptake of complement combining components by specific precipitates of S III was complete in 1 hr. at room temperature. This is in good agreement with the observation (73) that the fixation of the individual components as judged by functional tests is complete in 1 hr. These authors also showed that the combining nitrogen from guinea pig serum is the same regardless of whether the specific precipitates contain excess antibody or antigen. Of special interest was their finding that the amount of additive nitrogen combining with specific precipitates is independent of the weight of the specific antigen–antibody precipitates. The above information appeared to confirm Heidelberger's statement that the estimation of the combining nitrogen from fresh serum is a measure of complement or of its combining components in weight units. However (75), there is evidence that this measurement of complement nitrogen does not represent the total complement combining nitrogen present in serum unless data on the amount of activity of each individual component removed during fixation indicate that this is so. Heidelberger (39) noted that, although the absolute amounts of combining complement nitrogen are less when small samples of serum are used (5 ml. or under), the quantity of combining nitrogen per milliliter of guinea pig serum added is larger. Because of this fact, Heidelberger was unable definitely to determine the absolute amount of complement combining nitrogen per milliliter of guinea pig serum. Nevertheless, rough extrapolation of his data to zero volume gave 0.04 to 0.06 mg. of nitrogen or 0.25 to 0.40 mg. of protein as the amount of combining complement actually present in 1 ml. of guinea pig serum. Heidelberger (42) extended these studies to include human serum as the source of complement and found that human serum contributes from 0.03 to 0.05 mg. of complement nitrogen per milliliter of serum. However, even more so than in the case of guinea pig complement, the amount of fresh human serum nitrogen adding to specific precipitates bore little relation to the hemolytic titers of the various sera tested. Heidelberger (42) has called attention to the fact that the combination of appreciable amounts of complement components with antigen–antibody systems may complicate the interpretation of quantitative precipitin reactions in human sera. As this author states, "It is quite likely that small quantities of antibody, such as might occur during convalescence or after active immunization, could easily appear to be doubled by the C′N fixed during combination of the antibody with antigen and thus indicate too high an antibody content." ... "Therefore it appears best, ... to remove C′ by the method used in the experiments referred to, namely, by adsorption with adequate amounts of an unrelated precipitating system. . . ."

Experimental evidence (75) has been presented which shows that the estimation of the fresh serum nitrogen which adds to specific precipitates is a measure of a variable portion of the total complement complex. The results of this study, which correlated the quantity in weight units of fresh guinea pig serum nitrogen adding to specific precipitates with a measurement of the residual activity of each complement component after this combination, have helped to clarify data on the quantitative complement component combining nitrogen. It has been found, when such parallel studies were performed, that C′1, C′2, and C′4 from whole fresh serum all contribute varying amounts of combining nitrogen to specific precipitates. In agreement with Heidelberger's data it was noted that midpiece also contributes combining nitrogen, while endpiece of complement does not add nitrogen to the specific aggregates. It was shown also that C′1 of midpiece or whole serum contributes combining nitrogen; C′2 and C′4 furnish no additive nitrogen in the absence of C′1; and C′3 contributes little or no nitrogen in any case. Heidelberger, Bier, and Mayer have also shown that C′4 adds nitrogen to immune aggregates, and that C′3 contributes little or none.

As stated before, unless very small amounts of serum are fixed under rigidly controlled conditions, the total weight of the combining components is not measured. It has been shown that this is due primarily to a diminution in the fixation of C′1 when large amounts of complement are allowed to fix.

When small amounts of serum (1 ml.) are allowed to combine with specific precipitates, these usually contribute from 0.04 to 0.08 mg. of combining complement nitrogen per milliliter of serum. Heidelberger, by extrapolation, obtained quite similar values of 0.04 to 0.06 mg. of combining nitrogen per milliliter of serum. Purified C′1, as determined by actual isolation, comprises about 0.6 per cent of the total serum protein of the guinea pig, and each milliliter of serum contains about 0.06 mg. of C′1 nitrogen. Endpiece (C′2 and C′4) accounted for about 0.02 mg. of nitrogen per milliliter of serum. It is obvious that small deviations in the fixation of C′1 would markedly influence the complement combining nitrogen adding to specific precipitates. On the other hand, relatively large changes in the fixation of C′2 and C′4 would be necessary in order to influence significantly the total amount of nitrogen adding. Thus, although C′1, C′2, and C′4 all contribute to the combining nitrogen, C′1 appears to contribute most of the additive nitrogen.

C′1 is strongly attracted to specific precipitates. Indeed, heat activation of this component of complement does not remove its total combining capacity. Also in whole serum, heat inactivation does not destroy the total combining capacity of the serum. This effect, first noted by Ehrlich, is termed a "complementoid" effect, and is probably due to the differential temperature stabilities of the combining and functional hemolytic groups of C′1. It has therefore been suggested that the true combining nitrogen is the total nitrogen added from a definite volume of serum under controlled conditions, rather than the value obtained from the difference between the combining nitrogen of untreated serum and that from an equal volume of heat-inactivated serum (75).

Furthermore, recent evidence indicates that the total combining nitrogen contributed from fresh guinea pig serum to specific precipitates is an estimate of the amount of complement components combining under the conditions of the experiment, and is therefore a measure only of a variable portion of the total complement complex, and does not always represent the total combining capacity or the hemolytic activity of the total complement present. If, however, experiments determining the amount of activity of each component of complement removed during the fixation accompany the estimation of the combining nitrogen, accurate data may be obtained on the weights of the individual combining components.

In any event, studies along this line have established a definite approach to a problem which the more conventional trends have failed to clarify. As Heidelberger pointed out (39), while the quantitative methods employed in such experiments are too laborious and require too large volumes of serum to expect their widespread use for routine purposes, the techniques employed are useful for the acquisition of precise data, and should serve as tools for research and for the establishment of reference standards.

IMMUNE HEMOLYSIS

The most clearly defined property of complement is the hemolysis of sensitized red blood cells. Nevertheless, until recently, the rôle and function of the components of complement have not been clearly understood. As stated earlier in this review, Liefmann and Cohn assert that the disappearance of complement in immune hemolysis is due to the effect of hemolysis rather than to the initial fixation of complement. Eagle and Brewer and also Ponder have since shown that complement must first combine with the sensitized cell before hemolysis can occur.

Employing experimental conditions which were found to be optimal for the fixation of the components of complement by immune aggregates, it has been shown recently (74) that if the immune aggregate employed in fixation is a substrate which upon resuspension and appropriate treatment shows a visible manifestation, such as hemolysis, the nature and the rôle of the fixed components can be determined. The results of such experiments have helped to clarify the function of the components of complement in immune hemolysis and have revealed the following information: At temperatures of 1°C., C′1, C′2, and C′4 combine with sensitized sheep cells, while C′3 does not combine; C′1, although combining with sensitized cells in the absence of C′4, is hemolytically inert unless C′4 combines previously or simultaneously. In other words, the hemolytic activity of C′1 after fixation is predetermined by the fixation of C′4. Furthermore, C′4 does not combine in the absence of C′1; and in agreement with Nathan it was found that C′3 is not fixed by antibody–sheep cell aggregates, but is essential for hemolysis, operating on the sensitized cell after the fixation of C′4, C′2, and C′1 and behaving as if it were a catalyst. It has further been shown that the amount of C′1 which combines with sensitized cells is determined by the amount of C′4 available for fixation, that is, the more C′4 fixed by the cell, the less C′1 is needed to produce hemolysis and the less C′1 that is taken up by the sensitized cell. Indeed, only about 10 to 30 per cent of the actual amount of C′1 present in serum is utilized in the hemolysis of one unit of sensitized cells. The fixation of C′4 appears not only to predetermine the hemolytic activity of combining C′1, but also to determine the amount of C′1 that will fix and the amount that will be needed for hemolysis. This relationship, which has been hitherto unrecognized, indicates that a revision of existing thoughts on the interaction of complement, red cell, and antibody should be forthcoming.

Heidelberger (40) has attempted to trace the relationships of the combining complement to red cell and hemolysin in immune hemolysis. He was able to show that the complement combining components unite with antibody in equimolecular or even greater amounts. The interactions of sheep red cell stromata (43) with hemolysin result in the same amounts of complement being adsorbed as that taken out by other immune aggregates. The stroma combined with antibody takes up at least 80 per cent of its weight of complement combining components. Owing to the multiplicity of antibodies present in hemolysin and to the accessory components of complement which are not fixed but are utilized for hemolysis, Heidelberger concluded that his quantitative data have only limited application in the study of immune hemolysis. However, he was able to draw a reasonable picture of complement fixation. Accordingly, the combining components of complement are distinguished from normal serum globulins in that they possess one or more groupings capable of forming loose dissociable combinations with individual antibody and possibly antigen molecules, but which form firm combinations, dissociable with difficulty, when surrounded by great numbers of antibody or antigen molecules. Meanwhile, the following explanation of the action and rôle of the complement components in immune hemolysis appears the most plausible on the basis of existing data (74). Anti-sheep cell rabbit serum (hemolysin) by itself does not combine with or forms only loose dissociable unions with complement or any of its components, or at least does not inactivate them. Nevertheless, when the hemolysin combines with the red cell, the surface pattern of the antiserum molecule or the antiserum–cell aggregate changes and in turn different groups are in contact with the complement components, and firm combination then results between the specific aggregate and C′4, C′2, and C′1. C′4 combines first or simultaneously with C′1 to the red cell aggregates. The fixation of C′4 is accompanied by the fixation of C′2. The adsorption of these components in this definite order on the red-cell–antibody complex then renders the red cell amenable to the action of the unadsorbed C′3 and hemolysis results. Since C′3 is not taken up by the sensitized cell and is apparently not used up in the process of hemolysis, it appears to have certain enzymic qualities. This explanation, by no means complete, may serve as a working basis for continuance of studies along this line. Of course, actual isolation of all of the components of complement in sufficient quantities to subject them to thorough test will do much to clarify this as yet insufficiently explored field of immunochemistry.

SUMMARY

On the basis of the knowledge existing at this time, guinea pig complement can best be characterized as a composite of several serum entities: a euglobulin (C′1), a mucoeuglobulin which possesses both C′2 and C′4 activity, and a still uncharacterized component (C′3).

The interactions of these complement components with antigen–antibody compounds result in the combination of C′1, C′2, and C′4 with these compounds. In the red-cell–hemolysin system, C′4, C′1, and C′2 combine; after this combination, the red cell is rendered susceptible to the action of C′3, which behaves as if it were a catalyst, and hemolysis of the red cell occurs.

Recent advances in the study of the structure and function of the complement components served the purpose of elevating complement from the rank of a mysterious and elusive property of serum to the status of a composite of distinct chemical individuals, and may serve as a working basis for further exploration in this field.

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THE REACTION BETWEEN ETHYLENE DERIVATIVES AND THE HALOGENS

S. V. ANANTAKRISHNAN[1]
Madras Christian College, Tambaram, S. India

AND

R. VENKATARAMAN[2]
Annamalai University, Annamalainagar, S. India

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CONTENTS

I. Introduction 27
II. Reactions between olefins and fluorine 28
III. Reactions between olefins and chlorine 28
  A. Photochemical reactions 28
  B. Thermal reactions 31
IV. Reactions between olefins and bromine 32
  A. Photochemical reactions 32
  B. Thermal reactions 34
  C. Mechanism of the olefin–bromine reaction 36
  D. Influence of substituents 43
V. Reactions between olefins and iodine 46
VI. The general mechanism of the olefin–halogen reaction 49

I. INTRODUCTION

Considerable work on the addition reactions of olefins and the halogens has been published since the first preparation of ethylene dichloride by a group of Dutch workers (25), but a systematic investigation of the problem is comparatively recent history. The considerable industrial use of olefins and of their halogenated products in recent times has not been without its repercussions on the purely scientific side, and it is useful and necessary to consider the development of the subject and to survey the present position.

The greater part of the early work has been essentially of a qualitative nature, with no serious attempt to study the mechanism of the reaction. Also, an analysis of published work reveals that surprisingly few compounds have been the subject of study. The most important early work was on the reactions in the gaseous phase, between ethylene and chlorine and between ethylene and iodine, studied by Michael Faraday (29). In a remarkable communication to the Royal Society, Faraday observed that with equal proportions the addition reaction is complete, with excess olefin reaction stops after the addition, and with excess halogen substitution follows the addition reaction,—all the reactions being carried out in bright sunlight. Faraday observed that these reactions can also take place in the dark, though much more slowly. In the reaction between ethylene and iodine, however, the photochemical reaction appears to have stopped with the formation of addition compound, no hydrogen iodide being evolved.

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[1] Professor of Chemistry, Madras Christian College.

[2] Assistant Lecturer in Chemistry, Annamalai University.

Subsequent work in the nineteenth century does not indicate the same thoroughness of investigation. Generally carbon disulfide has been the solvent (30, 55, 56, 57, 59, 119, 120, 121, 122) in which the reactions were carried out. Carbon tetrachloride and chloroform have been used in some cases (13, 57, 66, 67). In the case of gaseous olefins, reactions in the gas phase were studied first. In all cases the addition compounds were obtained, and in some cases substitution products were found in connection with chlorine and bromine additions (7, 53, 84, 92). For convenience of treatment, the problem may be considered under various headings.

II. REACTIONS BETWEEN OLEFINS AND FLUORINE

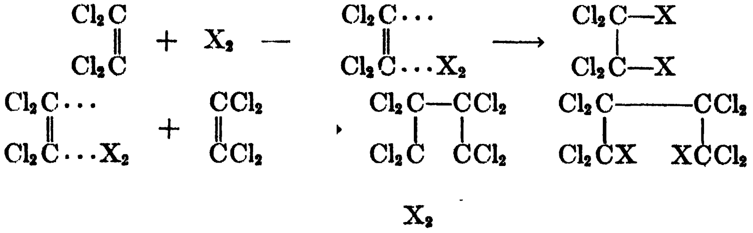
The considerable reactivity of fluorine has been a serious impediment in the study of the olefin–fluorine reaction. As may be expected, any fruitful results are possible only with comparatively inert olefins. Humiston and coworkers (45) observed that tetrachloroethylene reacts readily with fluorine, the products isolated being hexachloroethane, carbon tetrafluoride, and carbon. They suggested that the reaction probably proceeds as follows:—

$$C_2Cl_4 + 2F_2 \rightarrow 2Cl_2 + C_2F_4$$

$$C_2F_4 \rightarrow CF_4 + C$$

$$C_2Cl_4 + Cl_2 \rightarrow C_2Cl_6$$

The later investigations of Bockemüller (20) led to a somewhat different result. By the action of fluorine on a solution of tetrachloroethylene in dichlorodifluoromethane at −80°C. the addition compound, tetrachlorodifluoroethane, was formed, and also a by-product containing double the number of carbon atoms. To explain this behavior, following Meisenheimer (61) and taking into account the work of Hunter and Yohe (46) that provides some evidence for an activated olefin molecule with a free electron pair, the mechanism of the reaction was represented as follows:



III. REACTIONS BETWEEN OLEFINS AND CHLORINE

A. Photochemical reactions

Michael (63, 64, 65), Massot (49), and Kirchhoff (52) found addition reactions with very little side reactions occurring between the olefins studied by them and chlorine, in the presence of sunlight. In solution in carbon disulfide or carbon tetrachloride, Liebermann (57) found that the cinnamic acid–chlorine reaction gave a mixture of optical isomerides. Later Nasarow (73) observed that the reaction between cinnamic acid and chlorine in carbon tetrachloride takes place fairly rapidly even in the dark and showed that, for any temperature, the dark reaction must be separated from the total reaction. Taking this into account, he obtained for the photochemical reaction a temperature coefficient of 1.402. A more complete investigation was carried out by Berthoud and Porret (17). They found that the photochemical addition of chlorine is approximately independent of acid concentration, is proportional to the concentration of chlorine, and is a function of the light intensity. The results obtained by these workers differed from those of Basu (9), who suggested an atom-chain mechanism, in which the length of the chain is proportional to the energy of the monochloro compound formed in the first stage of the reaction. The later workers obtained a value of the quantum yield as variable, about 2.4, and a thermal temperature coefficient of 1.5. Following the work on bromine addition, these workers suggested the following chain mechanism to explain their results:

$$Cl_2 + h\nu \rightarrow Cl + Cl$$

$$A + Cl \rightarrow ACl$$

$$ACl + Cl_2 \rightarrow ACl_2 + Cl$$

$$2ACl \rightarrow X$$

In consideration of the complex nature of the substituents in cinnamic acid, it may be expected that olefin hydrocarbons and halogenated olefins may give better information on the mechanistic side. With the exception of ethylene and tetrachloroethylene, work in this direction has been practically nil.

Stewart and Weidenbaum (108a), working with methylethylethylene, found that the photochemical reaction involves both substitution and addition. They made the rather surprising observation that substitution is favored by increased olefin concentration, while an increased chlorine concentration favors addition. Stewart and coworkers (103, 106, 107, 108, 108a) have made a thorough study of this reaction, an investigation ranging over several years. In an early work (106) the observation was made that both addition and substitution reactions take place, the addition reaction inducing the substitution. In the absence of moisture and light the reaction is found to be autocatalytic, oxygen functioning as an inhibitor. A chain mechanism involving activated molecules is also suggested for the thermal reaction. The later photochemical investigations showed that the reaction is proportional to the concentration of chlorine at constant intensity of light and independent of the concentration of ethylene. There is the significant observation that in a mixture of hydrogen, chlorine, and ethylene, while no hydrogen reacted, the ethylene–chlorine reaction went to completion both in the dark and in light. The addition compound functioning as a solvent enhanced the reaction rate, reducing the extent of substitution. There is in pentane solution a high degree of substitution, the extent depending on the ethylene–chlorine ratio. Two alternative mechanisms leading to the same kinetic equation

$$-\frac{d(Cl_2)}{dt} = kI_{abs.} = kI_0(Cl_2)$$

have been suggested.

$$Cl_2 + h\nu \rightarrow 2Cl$$

$$\begin{array}{ll}
Cl + Cl_2 \rightarrow Cl_3 & Cl + C_2H_4 \rightarrow C_2H_4Cl \\
Cl_3 + C_2H_4 \rightarrow C_2H_4Cl_3 & Cl_2 + C_2H_4Cl \rightarrow C_2H_4Cl_3 \\
C_2H_4Cl_3 \rightarrow C_2H_4Cl_2 + Cl & C_2H_4Cl_3 \rightarrow C_2H_4Cl_2 + Cl \\
C_2H_4Cl_3 + \text{wall} \rightarrow C_2H_4Cl_2 + \frac{1}{2}Cl_2 & C_2H_4Cl_3 + \text{wall} \rightarrow C_2H_4Cl_2 + \frac{1}{2}Cl_2
\end{array}$$

While one has to admit that an atom-chain mechanism is most likely in the photochemical reaction, it is rather difficult to explain how there is no reaction with hydrogen, when it is used as a diluent. Presumably the lower energy of activation of 3 kilocalories for the over-all reaction arrived at by Sherman, Quimby, and Sutherland (101) provides one reason for the addition reaction taking precedence.

The photochlorination of the *cis*- and *trans*-dichloroethylenes has been thoroughly investigated by Müller and Schumacher (70, 71), using light of 4360 Å. between 80° and 95°C., the reactant concentration being maintained below a pressure of 100 mm. With an absorption rate of 10 to 15 quanta per minute, the quantum yield is given as 7×10^3 molecules. These authors observe that the reactions of both the *cis* and the *trans* forms are similar, with the same absolute velocity. At low pressures, below 20 mm., the reaction seems to be influenced by olefin concentration, but at higher pressures the velocity equation is given as

$$+\frac{d(C_2H_2Cl_4)}{dt} = kI^{1/2}_{abs.}(Cl_2)$$

Oxygen is observed to have a marked retarding influence and in the chain mechanism suggested by the authors it is presumed to react with ACl radicals. These authors observed a similar effect in the photochlorination of trichloroethylene. While with our present knowledge it is not possible to arrive quantitatively at the extent of mutual group interactions in influencing the additive reactivity of the double bond, it seems rather strange that with two olefins of widely different dipole moments, no difference in reactivity should be observed. The authors have been able to confirm in a later paper (71) the observation on the influence of oxygen by the isolation of oxygenated compounds. With a low temperature coefficient and a quantum yield of 40, a chain mechanism is suggested involving the formation of a peroxide. The interpretation, however, is complicated by the formation of carbon dioxide, phosgene etc.

Dickinson and coworkers (26, 27, 28) have studied the photochlorination of ethylene both in the gaseous phase and in solution. In both cases, in the absence of oxygen, the quantum yields were of the order of several hundred, and the best interpretation is possibly by a mechanism identical with that of Berthoud and Béraneck (15, 16).

$$\begin{array}{lll}
(1) & Cl_2 + h\nu \rightarrow 2Cl & \phi I_a \\
(2) & C_2Cl_4 + Cl \rightarrow C_2Cl_5 & k_2 \\
(4) & C_2Cl_5 + Cl_2 \rightarrow C_2Cl_6 + Cl & k_4 \\
(6) & Cl + Cl \rightarrow Cl_2 & k_6 \\
(7) & Cl + C_2Cl_5 \rightarrow C_2Cl_6 & k_7 \\
(8) & 2C_2Cl_5 \rightarrow C_2Cl_4 + C_2Cl_6 & k_8 \\
 & \text{or} & \\
 & 2C_2Cl_4 + Cl_2 &
\end{array}$$

The non-appearance of the olefin concentration in the reaction-rate equation indicates that every chlorine atom reacts according to equation 2. The observation by Müller and Schumacher (70, 71) of a pressure limit when the olefin concentration affects the reaction, evidently represents the lower limit of concentration at which all chlorine atoms may be expected to react by reaction 2. The inhibitory effect of oxygen and the detection of carbonyl chloride bring this in line with other observations on like reactions. In the presence of oxygen, even at 40°C., there is no perceptible reaction, while in the absence of it there is slight thermal reaction. These authors suggest an alternative method of formulating the mechanism, though Berthoud's mechanism may account for the observations equally well.

B. Thermal reactions

While the photochemical reactions appear to have been well investigated, the studies of the thermal reactions are very few and comparatively recent. Norrish and Jones (75) observed the remarkable effect of the nature of the reaction surface on the gas reaction; they found that the reaction proceeds only in the presence of a polar surface and that the thermal reaction is essentially heterogeneous with apparently no homogeneous reaction.

In dissociating solvents like acetic acid and nitrobenzene (97), the addition of chlorine to *cis*- and *trans*-cinnamic acids gives bimolecular constants, the *cis* acid adding nearly four times faster than the *trans* acid. While dilution appears to have no effect on the value of k_2 in both solvents, the constants tend to diminish with increased dilution in the case of the *trans* acid. The bearing of this and of the values of the Arrhenius parameters on the mechanism is discussed in greater detail in a later section.

Mention should also be made of Tishchenko's work (113) on tetrasubstituted ethylenes. The results indicate that the polarization of the double bond at the quaternary atom leads to anomalous reaction with chlorine. With increasing number of chlorine atoms in the alkyls attached to the quaternary carbon atom, addition increases, while substitution diminishes.

A comparison of the thermal and photochemical reactions with the meager data available indicates an apparently clear-cut demarcation between the two types. The photochemical change appears essentially to depend on the dissociation of the chlorine molecules into atoms with chains involving atomic chlorine, while the thermal reaction probably proceeds by a mechanism involving molecular chlorine.

IV. REACTIONS BETWEEN OLEFINS AND BROMINE

A. Photochemical reactions

While the olefin–chlorine reaction has been studied in the presence of light to a considerable extent, controlled photochemical reactions between olefins and bromine have been studied in comparatively few cases. The work done, however, is sufficient to indicate that the photochemical reactions involving the halogens are essentially similar, though the exact mechanisms may differ.

The preliminary observations of Sudborough and Thomas (109, 110, 111) indicate the enormous influence exerted by light on this reaction. The results of Hofmann and Kirmreuther (43), though comparable amongst themselves, can at best be taken only as qualitative, since the photochemical reactions have not been studied under sufficiently rigidly controlled conditions. The work of Plotnikow (81, 82, 83) on the reactions between bromine and compounds of the structure $R_1R_2C{=}CR_3R_4$ led to the following conclusions: the reaction appears to be in equilibrium which depends upon temperature, the temperature coefficient being of the order of 1.4; the concentration of the reactants, the solvent, the intensity of light (the reaction rate varying as the square of the intensity of light), and the nature of the substituents (R_1, R_2, R_3, and R_4) affect the reaction rate. Plotnikow considers that in the photochemical reaction bromine atoms are definitely involved.

The most thoroughly investigated reactions have been with cinnamic acid, stilbene, and tetrachloroethylene. In a thorough and comprehensive study, Berthoud and coworkers (15, 16) found that, for strong absorption of light, the reaction rate was found to accord with the equation

$$-\frac{d(Br_2)}{dt} = k'I_0^{1/2}(Br_2)$$

and for weak absorption it is

$$k''I_0^{1/2}(Br_2)^{3/2}$$

wherein I_0 stands for the intensity of the incident light. The experimental data indicate clearly a chain mechanism and these authors suggest the following scheme:

$$(1)\quad Br_2 + h\nu \rightarrow 2Br \qquad I_{abs.}$$

$$(2)\quad A + Br \rightarrow ABr \qquad k_2$$

$$(4)\quad ABr + Br_2 \rightarrow ABr_2 + Br \qquad k_4$$

$$(6)\quad Br + Br \rightarrow Br_2 \qquad k_6$$

$$(7)\quad ABr + Br \rightarrow ABr_2 \qquad k_7$$

$$(8)\quad ABr + ABr \rightarrow ABr_2 + A \qquad k_8$$

or

$$2A + Br_2$$

It is clear that the primary process involves the dissociation of the bromine molecule into atoms, while the proportionality of the rate constant with bromine concentration indicates that the rate-determining step involves bromine molecules. These authors consider that the velocity constant is independent of the olefin concentration, but an examination of the values shows a progressive fall with decreasing concentration of olefin. Reactions 2 and 4 constitute the chain, while reactions 6, 7, and 8 serve as chain-terminating steps. Since the reaction appears to depend essentially on the halogen concentration, reaction 4 is probably the rate-determining step, while reaction 2 is relatively fast. Also, if reaction 2 is sufficiently fast, the chain-breaking mechanisms 6 and 7 may be neglected compared with reaction 8. The non-appearance of the olefin concentration in the experimental equation of these authors indicates that this is largely true. Hence the reaction-velocity equation may be written as

$$-\frac{d(Br_2)}{dt} = I_a + k_4(ABr)(Br_2)$$

For the stationary state,

$$(ABr) = \frac{\phi^{1/2} I_a^{1/2}}{k_4^{1/2}}$$

and hence

$$-\frac{d(Br_2)}{dt} = I_a + \frac{k_4 \phi^{1/2}}{k_4^{1/2}} I_a^{1/2}(Br_2)$$

This equation will agree with the experimental rate equation for long chains, i.e., where the chain-breaking mechanism (reaction 8) is negligible when compared with reaction 4. It is interesting to note that *trans*-cinnamic acid, apparently the compound used by these authors, reacts approximately at the same rate as stilbene. These authors' figures for the velocity constant led to a value of the energy of activation for the reaction of 11,500 calories for cinnamic acid in carbon tetrachloride.

Bauer and Daniels (12) have examined the photobromination of cinnamic acid from 0° to 30°C. and over a concentration range of 2×10^{-3} to 8×10^{-3} moles per liter. Their results clearly indicate again a chain mechanism with varying quantum efficiency from 1 to 15, dependent on bromine concentration as well as temperature. The primary photochemical process involves the activation of a bromine molecule, and this is followed by a photoexcited thermal reaction. This thermal reaction, measured by $\phi - 1 = \theta$, is suppressed either by dilution of bromine or by low temperature. A linear relationship between log θ and the reciprocal of the absolute temperature is considered to support the energy chain mechanism.

$$Br_2 + h\nu = Br_2^*$$

$$Br_2^* + A = ABr_2'$$

$$ABr_2' + Br_2 = Br_2'' + ABr_2$$

$$Br_2'' + A = ABr_2''$$

$$ABr_2'' + Br_2 = Br_2''' + ABr_2$$

Later work by Willard and Daniels (23) with tetrachloroethylene, together with their own work on cinnamic acid (12), appears to indicate the pronounced inhibitory effect of oxygen on the course of the reaction; in fact, in the absence of oxygen the thermal bromination of cinnamic acid is too fast to measure. This mechanism, together with those of Ghosh and Purkayastha (37), are dealt with in detail in a later section. The work of Purkayastha (89) is, however, of doubtful value in understanding the course of the reaction. One finds a rather surprising statement that "this period of gradually increasing velocity is called the period of induction," and the calculations indicated in the paper, neglecting the induction period in the accepted sense of the term, obviously cannot lead to a correct conclusion.

B. *Thermal reactions*

The first important observation is that of Plotnikow (80), who studied the bromination of ethylene in the dark in petroleum ether at −78° to −100°C. and obtained the results shown in tables 1 and 2. The reaction was followed by observing the change in volume of the reactants. When only one reactant was in excess, a unimolecular constant was obtained, while with both in comparable proportions, bimolecular constants were obtained. This author, however, reports a reaction giving rising constants, but does not investigate the question of catalysis. In the light of later observations (1, 3, 4, 115), these results may be interpreted as arising from the presence, in all but one case, of adequate amounts of the catalyst, hydrogen bromide, to eliminate both induction period and autocatalysis. There is also this further complication that in the non-polar solvent (petroleum ether) used, there is a possibility of a heterogeneous reaction.

TABLE 1

Bromination of ethylene

ETHYLENE	BROMINE	VELOCITY CONSTANT k_1
a = constant	b = 0.024 moles/liter	0.19
a = constant	b = 0.0201 moles/liter	0.17
a = constant	b = 0.0143 moles/liter	0.24
a = 0.0327 moles/liter	b = constant	0.35

The observations of Stewart (104) of the same reaction in the gas phase in the presence of oxygen indicate an essentially heterogeneous reaction with practically no evidence for the homogeneous part. With a constant surface, the reaction rate was found to be proportional to the concentration of reactants, there being no deviation from a bimolecular reaction. Water vapor was found to catalyze the reaction and the initial rate appeared to be greater than the later course of the reaction, an abnormality which the author attributed to wall catalysis. The heterogeneous nature of the gaseous reaction has been confirmed by Norrish (74), who has clearly established the close correlation between the reaction rate and the polar nature of the surface. In a later paper, Stewart (105) observed autocatalysis in the same reaction and also obtained a negative temperature coefficient. This is indicative of a trimolecular mechanism for the heterogeneous reaction.

A more complete investigation by G. Williams (117) of the surface reaction at room temperature in glass vessels indicated a simple addition reaction, followed by supplementary reactions when the bromine is in excess, a behavior recalling the observations of Faraday (29). The kinetics of the reaction was found to be complex, with a negative temperature coefficient and an order of reaction varying with the surface. This author has provided clear evidence that the reaction involves more than one stage. For a given surface, reduction of temperature or increase of pressure of the reactants appears to lower the order of the reaction, while for a given surface and reaction order, the rate constant appears to depend only on the bromine concentration. The catalytic effect of water was pronounced, and it was found that the transition from the second- to the first-order kinetics is favored by a wet surface and a high bromine–ethylene ratio. The product of the reaction is also reported to increase the rate, besides inducing a homogeneous reaction.

TABLE 2

Bromination of ethylene

ETHYLENE	BROMINE	VELOCITY CONSTANT k_3
moles per liter	*moles per liter*	
0.0451	0.0362	6.6
0.0126	0.0126	6 8
0.01885	0.01885	6.4

The work on chloroethylenes (42) is not sufficiently accurate to warrant conclusions as to the nature of the addition reaction. The results of Herz and Rathmann indicated an induction period of about 800 min. with tetrachloroethylene, but the results on di- and tri-chloroethylenes were different, the difference being obviously due to uncontrolled catalytic conditions. The recent investigations of G. Williams (118) on vinyl bromide constitute an important advance in our knowledge of the reaction in the gas phase. The exact mechanism is discussed in relation to the reaction in solution later, but it may be stated here that the study has shown that the reaction is a trimolecular one, is heterogeneous, and involves molecular and not atomic bromine.

In an earlier communication Williams and James (116), from a study of the addition of bromine to a number of unsaturated acids like cinnamylideneacetic, crotonic, and cinnamic acids and their derivatives in chloroform and carbon tetrachloride, divided the reactions into three groups: (*1*) rapid addition followed by substitution accounting for the production of hydrogen bromide with falling k_2 values, e.g., in the case of cinnamylideneacetic acid; (*2*) a slow but measurable addition with an induction period, e.g., in the cases of crotonic and cinnamic acids; (*3*) no measurable addition under the conditions investigated.

These authors found that hydrogen bromide was an effective catalyst, and considered that the mechanism of the dark reaction is different from that of the photochemical one. While the results reported appear to indicate that the reaction in both solvents is homogeneous, the experiments in carbon tetrachloride may not be expected to be so. In a subsequent communication (50) James has shown that the three isomorphic forms of *cis*-cinnamic acid react at the same rate, contrary to the observations of Meyer and Pukall (62).

The first observation leading to doubt as to the correctness of all the earlier work was that of D. M. Williams (115), who clearly demonstrated that with ethylene in carbon tetrachloride the addition reaction shows a clear induction period of many minutes depending on the concentration of bromine (11 min. in one case), and the curve drawn from his data shows all the characteristics of a chain reaction (reference 4, page 293). This observation has been confirmed by Anantakrishnan and Ingold (1). Using acetic acid as solvent, Williams obtained apparently bimolecular constants, the deviation from this being more marked with rise of temperature. In interpreting his results, Williams stated that "the addition of the acetoxy group instead of the second bromine does not take place to a detectable extent." This is to be expected, in view of the observations of Hennion, Vogt, and Weber (39), if the solution had initially contained any hydrogen bromide. We find qualitative evidence in the case of bromine additions, confirming the observations of Hennion and coworkers, to the effect that Williams' statement that the intermediate production of hydrogen bromide is not sufficient to account for the fact that there is no inhibition period when the addition occurs in acetic acid requires revision (3, 4, 95). It is our experience that unless rigid care is exercised to exclude moisture and hydrogen bromide from the reactants the inhibition period fails to be noticed.

It is necessary to mention here that the choice of solvent is extremely important in following the reactions in solution. Alcohols and esters which are definitely known to react with bromine are unsuitable for any mechanistic studies or interpretation of group influences, while non-polar solvents like carbon tetrachloride and carbon disulfide, which might approximate to the conditions in the gas phase, suffer from the handicap of a possible non-homogeneity in the reactions in solution. Under controlled conditions at ordinary temperatures, the best solvents appear to be methylene chloride, chloroform, and acetic acid.

C. Mechanism of the olefin–bromine reaction

Though in the case of a decomposition like that of nitrogen pentoxide the reaction in the gas phase and in solution, as well as thermal and photochemical reactions, follows more or less the same mechanism, in the case of reactions like the present some difference may be expected. The work of Francis and of Terry and Eichelberger (33, 112) has clearly demonstrated that in halogen additions in solution, it is only molecular bromine that takes part in the reaction. Also the conditions of the dark reaction could reasonably be expected to involve the activated bromine molecule rather than atomic bromine, though addition may take place in stages.

For the photochemical reaction, three main mechanisms have been suggested,—the mechanisms of Berthoud and Béraneck (*loc. cit.*), of Ghosh and coworkers, and of Daniels and coworkers. The mechanism suggested by Daniels and Bauer has already been given; the modified mechanism suggested by Daniels and Willard in their later communication, and the mechanism of Ghosh and coworkers are given below.

Mechanism of
Ghosh and coworkers (36)

$$\text{(1)}\quad Br_2 + h\nu \rightarrow 2Br$$

$$\text{(2)}\quad Br + Br \rightarrow Br_2$$

$$\text{(3, 4)}\quad Br + Br_2 \rightleftarrows Br_3$$

$$\text{(5)}\quad Br_3 + A \rightarrow ABr_2 + Br$$

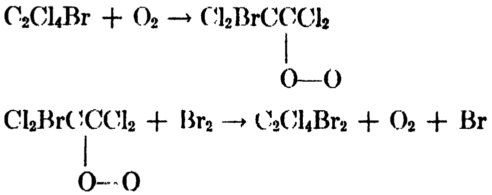
Mechanism of
Willard and Daniels (23)

$$Br_2 + h\nu \rightarrow Br + Br$$

$$C_2Cl_4 + Br \rightleftarrows C_2Cl_4Br$$

$$C_2Cl_4Br + Br_2 \rightleftarrows C_2Cl_4Br_2 + Br$$

$$Br + Br \rightarrow Br_2$$



$$C_2Cl_4Br + O_2 \rightarrow Cl_2BrCCCl_2(O{-}O)$$

$$Cl_2BrCCCl_2(O{-}O) + Br_2 \rightarrow C_2Cl_4Br_2 + O_2 + Br$$

The mechanism of Berthoud suffers from the disability that it involves small temperature coefficients. Daniels has shown that Ghosh's mechanism is difficult to maintain, as the energy of addition of Br_3 to the double bond will be greater than that of Br_2 by about 10,000 calories. Further, the mechanism suggested leads to a rate law of the form

$$-\frac{d(Br_2)}{dt} = k_3\left[\frac{I_{abs.}}{k_2}\right]^{1/2}(Br_2)\,\frac{k_5(A)}{k_5(A) + k_4}$$

The last factor on the right-hand side could be tested only by a sufficient variation of experimental conditions, and in the absence of such evidence it is possible to fit in their results with other mechanisms as well. The formation of Br_3 molecules involves an energy of activation of 10,000 calories, which is approximately the difference between the $^2P_{3/2}$ and $^2P_{1/2}$ states of the bromine atom, but this observation of Ghosh is not of much significance, since we do not have any experimental evidence to lead us to the conclusion that the $^2P_{1/2}$ bromine is more reactive than $^2P_{3/2}$.

In order to account for the course of the addition reaction, together with the inhibitory effect of oxygen on the photochemical reaction, Daniels and Willard (23) have suggested a mechanism taking into account the fact that the product of the reaction has an inhibitory effect as well. With tetrachloroethylene as the olefin, the concentration of the unsaturated compound does not appear to be involved in the rate, and the photochemical reaction appears to have a very small temperature coefficient. The mechanism involves a free radical containing a bromo compound, and this intermediate is considered to explain also the reversibility of the reaction at higher temperatures. While small amounts of oxygen accelerate the photobromination, large amounts have the reverse effect, presumably owing to photosensitized oxidation.

From his study of the heterogeneous gas reaction in the dark, Norrish (74) was led to conclude that the reaction consists in the polarizing of the reactant molecules by *association with a polar catalyst* either in gaseous, surface, or liquid phase. The kinetic studies of G. Williams (117) again indicate a chain mechanism, and in order to account for the apparent effect of water, he suggested a bromine–water complex, adsorbed on the glass surface, which reacts with ethylene. While Daniels found for the photochemical reaction that the products had an inhibitory effect, Williams noted that the products increased the rate of reaction. But Kinumaki *et al.* (51) appear to have found that, even in the dark reaction, the results are the same as those of Daniels. The only other study in the gaseous phase with a view to elucidation of the mechanism is that of G. Williams (118), who investigated the reaction between vinyl bromide and bromine. He found for the rate expression the equation,

$$-\frac{dx}{dt} = (\text{olefin})(\text{Br}_2)^2 k_3$$

the heterogeneous reaction having a negative temperature coefficient. With the olefin in excess, an apparent bimolecular constant is obtained, while in other cases an initial rapid reaction of the third order, followed by a reduced reaction of the third order, appears to result. Inert surfaces, however, require a different rate expression,

$$-\frac{dx}{dt} = k_2(\text{olefin})(\text{Br}_2)$$

while the introduction of water vapor restores third-order kinetics. The following mechanism has been suggested to account for the observations:

$$\text{Olefin} + \text{Br}_2 \rightarrow \text{Intermediate complex}$$

$$\text{Intermediate complex} \rightarrow \text{Dibromo compound}$$

While this mechanism probably explains the gas reaction, which is essentially heterogeneous, the homogeneous reaction in solution in polar solvents may not conform to it.

With the available evidence it is very difficult to decide whether the dark reactions in non-polar solvents like carbon tetrachloride and carbon disulfide are to be considered homogeneous or heterogeneous. The observations of D. M. Williams, which show all the characteristics of a chain reaction, can, however, be considered so far as the positive catalytic effect of hydrogen bromide is concerned. With polar solvents the reaction appears to be clearly homogeneous, and these reactions therefore lend themselves to clearer mechanistic studies. The alternative mechanisms that have been proposed are essentially those of Robertson and coworkers, and those of the authors of this review.

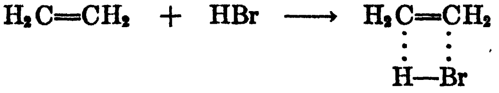
It is relevant to mention here that the reactions studied for elucidating the mechanism have all been with α,β-unsaturated acids. It has been observed (60, 98) that the reaction is not influenced by oxygen or peroxides, so that any mechanism suggested may ignore for the present the peroxide effect, observed with simple olefins in gaseous photochemical reactions.

All earlier work on the olefin–bromine reaction gave bimolecular constants and pseudo-monomolecular constants with one of the reactants in excess. That this is no true representation of the actual reaction is seen when one examines the observations of Plotnikow, who obtained rising constants, and the vagarious constants obtained by Herz and Mylius (40, 41), Hofmann and Kirmreuther (43), and Sudborough and Thomas (109, 110, 111). Even in the case of the gas reactions, whether thermal or photochemical, work during the last decade has reduced the number of apparently simple bimolecular reactions to two. It is not, therefore, unlikely that in solutions also one has to expect a similar state of affairs. Systematic work on many reactions in solutions involving organic compounds has shown that these earlier notions, which ascribed simple mechanisms to them, must give place to chain mechanisms involving atoms, free radicals, and activated complexes (98).

Robertson *et al.* consider that the reactions between halogens and olefins involve a trimolecular mechanism and suggest that it is probably similar to that of G. Williams. Taking the reaction between bromine and *cis*- and *trans*-cinnamic acids, in both acetic acid and carbon tetrachloride, it is suggested that in the polar solvent the velocity depends on (*1*) the rate of conversion of the *trans* to the *cis* form, (*2*) the rate of addition to the *trans* form, and (*3*) the rate of addition to the *cis* form. The function of hydrogen bromide is considered to be to accelerate the isomeric change. The experiments in carbon tetrachloride indicate a heterogeneous reaction below 50°C. and a homogeneous trimolecular reaction above that. These authors remark that hydrogen bromide is not a catalyst in the addition of bromine to *cis*-cinnamic acid. The case of acrylic acid, however, seems to provide the difficulty. So far as aliphatic unsaturated compounds are concerned we are unable to get trimolecular constants, the catalyzed reactions invariably giving good bimolecular constants. The difference might be attributed partly to the purity of bromine employed. The elimination of hydrogen bromide is a difficult process, and in most cases the experimental details do not indicate that this catalyst had been eliminated from the bromine used. In all cases that we have examined, a very clear, strictly reproducible, and well-defined period of induction is observed, and this varies with the nature of the groups attached to the olefinic linkage. Activating groups in general diminish the induction period, while deactivating groups have the opposite effect.

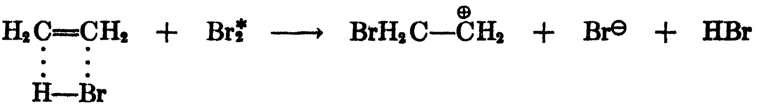
A trimolecular reaction does not necessarily preclude binary intermediate compounds. The problem can logically be simplified by considering that a binary collision may involve a certain duration whether an association compound is formed or not, this duration being a function of the structure of the molecules and of intermolecular forces. This complex formed may then be involved in a collision with a further molecule in the process. Considered in this form the trimolecular mechanism of Robertson reduces to the following mechanism proposed by us (3):

(1) $H_2C{=}CH_2 + Br_2 \longrightarrow CH_2{=}CHBr + HBr$

(2) 

$$H_2C{=}CH_2 + HBr \longrightarrow \begin{array}{c} H_2C{=}CH_2 \\ \vdots \quad \vdots \\ H{-}Br \end{array}$$

(3) $HBr + Br_2 \longrightarrow HBr + Br_2^*$

(4) 

$$\begin{array}{c} H_2C{=}CH_2 \\ \vdots \quad \vdots \\ H{-}Br \end{array} + Br_2^* \longrightarrow BrH_2C{-}\overset{\oplus}{C}H_2 + Br^{\ominus} + HBr$$

(5) $BrH_2C{-}\overset{\oplus}{C}H_2 + Br^{\ominus} \longrightarrow BrH_2C{-}CH_2Br$

This takes into account the definite and pronounced influence of hydrogen bromide on the reaction, at any rate in polar solvents. In the association complex that is formed, the place of hydrogen bromide may be taken by any other catalyst, like iodine chloride or quinoline. As we have pointed out (3, 4, 5, 114), the catalytic influence of any of these reagents is not the same for all compounds. The presence of sufficient activating groups attached to the olefin residue may reduce the need for external activation and the reaction may appear to obey second-order kinetics without the catalyst (see table 3). At lower temperatures none of the three acids gave any constants (Anantakrishnan and Venkataraman), though the induction periods clearly indicated the influence of activating groups. Table 3 demonstrates that the part of the catalyst can be eliminated if adequate structural and thermal activations are present. It may be logical to expect that similar apparent bimolecular reactions may become possible even at low temperatures with suitable substituents. Under such conditions it may become difficult to distinguish between this chain mechanism and the one suggested by G. Williams.

While considering the problem of mechanism it is necessary to see whether the initiation of addition is by positive halogen or by negative. As indicated earlier, the work of Francis (33) and of Terry and Eichelberger (112) suggests the positive halogen as the initiator. From *a priori* considerations and from the experimental evidence in which activating groups are systematically introduced, Ingold and coworkers have shown that the existing observations are best reconciled by adopting the same view. Ogg (76), however, questions the validity of the above mechanism of Ingold (47) and the slightly modified mechanism of Carothers (22), on the ground that it leads one to expect identical products—a mixture of meso and *dl* halides from *cis–trans* isomers, contrary to experimental evidence. Also he has suggested the following mechanism in which addition is initiated by negative bromine:

$$CHR{=}CHR + Br^{\ominus} \rightarrow CHRBr{-}\overset{\ominus}{C}HR$$

$$RHBrC{-}\overset{\ominus}{C}HR + Br{-}Br \rightarrow RCHBr{-}HCRBr + Br^{\ominus}$$

This mechanism requires catalysis by bromide ions, which is apparently supported by earlier work. Ogg considers that his mechanism explains the stability of the intermediate compound, the formation of stereoisomeric addition products from *cis–trans* isomers, and the generally observed *trans* addition of halogens. His contentions, however, are difficult to maintain. The observed influence of substituents on additive reactivity is not compatible with initiation of attack by negative halogen except where an "electron sink" is attached to the olefin residue. Also in the case of non-aqueous solvents, where ionization of hydrogen bromide may not be expected, the catalytic influence cannot be as simple as the one postulated by Ogg.

Further, Roberts and Kimball (93), in attempting to explain the results of Bartlett and Tarbell (8), postulated for the intermediate compound a structure of the ethylene oxide type as an improvement over the ones suggested by Robinson (97a) and by Ingold (47). These authors consider "that free rotation about the C—C bond is not to be expected. If this structure is assumed one of the orbitals of C^+ must be completely empty. The X atom, on the other hand, has three orbitals occupied by pairs of electrons. The arrangement is such that a co-ordinate link will almost be certainly formed by sharing of one of the pairs of electrons of the halogen with the unoccupied orbital of the carbon. Another possible structure of the ion is one in which the positive charge is on the halogen. The X^+, being isoelectronic with a member of the oxygen family, should show a valence of two, i.e., it should form a structure of the ethylene oxide type

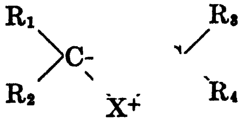
TABLE 3

The reaction between bromine and three α,β-unsaturated acids in acetic acid at 50°C.

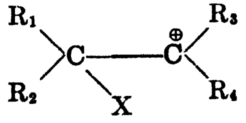
ACID	CONCENTRATION OF REACTANTS	CATALYST CONCENTRATION*	VALUES OF $100k_2$ FOR PER CENT REACTION					VALUES† OF k_3 FOR PER CENT REACTION				
			10%	15%	20%	30%	40%	10%	15%	20%	30%	40%
Crotonic ..	M/30	Nil	2.45	2.69	2.88	3 37	3.88	3.11	3.51	3.89	4.91	6.22
Crotonic .	M/30	11.01	9.06	8.62	8 52	8.67	8 85	11.5	11.3	11.5	12.6	14.2
Tiglic..	M/30	Nil	12.2	13.2	14.0	15.8		15.4	17.2	18.9	23.0	
Tiglic. . ..	M/30	11.01	30.3	31.2	31.5	31.4	30.3	38.4	40.7	42.5	45.7	48.5
β,β-Dimethylacrylic.	M/30	Nil	78.6	79.0	77.8	76.2	73.0	132	133	140	151	166
β,β-Dimethylacrylic ..	M/60	Nil	45.0	47.1	47.8	49.8	50.6	114	123	129	145	162

* Molar percentage of catalyst per mole of each reactant

† Concentrations are expressed in gram-moles per liter; unit of time, minute; values of k_3 are calculated using Robertson's equation (95).



II



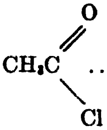
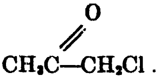
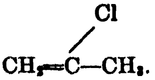
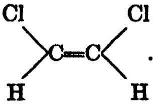
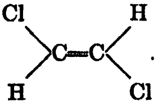
I

From the electronic point of view structures I and II are identical. The difference between the ionization potential of carbon (11.22 volts) and that of a halogen (e.g., 11.8 volts for bromine) is so small that the actual structure of the ion is undoubtedly between I and II. Since the two carbons in either structure are joined by a single bond and by a halogen bridge, a free rotation is not to be expected."

If, however, R_1 and R_3 or R_2 and R_4 are similarly charged groups (e.g., $COO^{\ominus}$), there may be sufficient repulsion between them to overcome the restraining force of the double linkage and rotation to the opposite configuration may take place before the second step of the reaction occurs. The ionization potentials of chlorine and of iodine are also not far removed from that of carbon, and a similar mechanism involving resonance between the two structures is possible for these halogens. The case of fluorine is different. The general *trans* addition is also explained by assuming the addition of X or some other atom or molecule to approach one of the carbon atoms from the side opposite to the X atom already present, thus being similar to the three-atom reaction type proposed by London

TABLE 4

Efficiencies of reaction of halides with sodium

COMPOUND	NUMBER OF COLLISIONS FOR ONE SUCCESSFUL TRANSFORMATION	COMPOUND	NUMBER OF COLLISIONS FOR ONE SUCCESSFUL TRANSFORMATION
CH_3I	1	 CH_3COCl	100
CH_3Br	50	 CH_3COCH_2Cl	10
CH_3Cl	10,000	$CH_2{=}CHCl$	11,000
CH_3F	10,000,000	 $CH_2{=}C(Cl){-}CH_3$	5,500
CH_3CH_2Cl	7,000		1,800
$(CH_3)_2CHCl$	3,300		2,600
$CH_3CH_2CH_2CH_2Cl$	3,300		
$(CH_3)_3CCl$	1,500		

(58) and developed by Polanyi (86, 87) and Olson (78, 79). This similarity probably accounts for the group influences on atomic reactions observed by Polanyi (85) which are analogous to their influence on olefin–halogen reactivity (see table 4).

It may not be out of place to mention here that the abnormally rapid addition of bromine to crotonaldehyde has been explained by Ingold and Anantakrishnan (2) as due to the initiation of attack by negative bromine, consequent on the development of a positive charge on the α-carbon atom due to the powerful electron-attracting carbonyl link. Compounds of this type may conform to Ogg's mechanism but it will be interesting to note if there are other such instances. Some work is in progress in these laboratories to test this aspect of the problem.

D. *Influence of substituents*

Before the advent of the electronic theory of organic reactions, very little quantitative work had been done on the influence of substituents on the rate of addition of halogens to ethylenic derivatives. Any little work done merely classified groups into two types, activating and deactivating. The degree of accuracy and the inadequate control of catalysis precluded any definite classification.

TABLE 5

Rate constants for the bromination of olefins

OLEFIN	RATE CONSTANT
Ethylene	0.006
Propylene	0.200
Isobutene (butene-2)	60
Trimethylethylene	250
Diisobutylene	20

Bauer and Moser (10, 11), from their studies on the addition of bromine to stilbene, methylstilbene, α-phenylcinnamonitrile, cinnamic acid, and bromocinnamic acid, found that C_6H_5, Br, COOH, and CN deactivate, while CH_3 probably activates. Sudborough and Thomas' experiments (109, 110, 111) on the rate of addition of bromine to a series of unsaturated acids, under uncontrolled catalytic conditions, indicated that the introduction of the methyl group facilitates addition, and that conjugated systems containing the carboxyl group and the α,β-ethylenic linkage react more readily than the simple ethylenic conjugated system. In addition, reference may be made to the several dynamical investigations on bromine addition by Herz and Mylius (40, 41), Brüner and Fischler (21), Hofmann and Kirmreuther (43), and Reich, Van Wijck, and Waelle (91). Davis was the first to give a quantitative idea of the effect of substituents. From his experiments on the olefin–bromine reaction he gave the data in table 5 for the comparative reactivity of methyl-substituted ethylenes.

Also, indications of a competitive method are found in Davis' procedure for studying the relative velocity of bromination.

The first important work on a quantitative study of the influence of substituents on the reactivity of ethylenic compounds is that of Ingold and coworkers (1, 2, 48). A competitive method was developed for the comparison of the reactivity, and it was found that the few necessary prerequisites for such comparisons are satisfied under the experimental conditions used (4). The relative rates of addition of bromine to ethylene and its simple derivatives were found to be consistent with theory and the possibility of an inverted mutual action, with several substituents, has also been demonstrated in one case (48).

From *a priori* considerations, taking into account related work on aromatic substitution and on tautomerism, Ingold and Ingold (48) classified substituent groups as shown in table 6. The work of Anantakrishnan and Ingold (*loc. cit.*) suggests that one may predict the comparative rate of addition of bromine to an ethenoid compound, if the effect exerted by each substituent is known quantitatively, in compounds with closely related structures.

TABLE 6

Classification of substituent groups

(1) $+I$

$:\!C \leftarrow CH_3$

(2) $-I$

$:\!C \rightarrow \overset{\oplus}{N}(CH_3)_3$

(3) $-I\ -T$

$\overset{\curvearrowright}{:\!C \rightarrow} COOH$

(4) $-I + T$

$:\!C \rightarrow \overset{\curvearrowleft}{Br}$

(5) $+I\ +T$

$:\!C \leftarrow O^{\ominus}$

(6) $+I\ -T$

$:\!C \leftarrow COO^{\ominus}$

(7) $\pm T$

$\underset{\curvearrowleft}{\overset{\curvearrowright}{:\!C \leftarrow}} C_6H_5$

In comparing the influence of substituents on additive reactivity, it is essential to bear in mind the rôle of solvent, catalyst, and temperature. In the same solvent, temperature may not exert any great influence on the reduced velocity (i.e., the ratio of the rate of reaction with a given substance relative to the rate with ethylene), if other conditions are the same (see table 7). A change of solvent, however, affects the values considerably. While the introduction of a methyl group at the same carbon atom in the case of propylene increases the velocity constant about threefold in methylene chloride solution, in the case of crotonic acid addition of a methyl group in a similar position increases the velocity constant twentyfold at 35.5°C. in acetic acid solution and about thirteenfold at 50°C. (i.e., for crotonic acid and dimethylacrylic acid). Though quantitative comparisons are not possible in the present stage of investigations, the difference is noteworthy. No doubt, a strict comparison of the two instances raises the question of mutual group interaction, arising from the complication of a carboxyl group, but solvent effect cannot be a negligible factor. The known formation of a complex with acetic acid by iodine suggests that some association of the bromine molecule with acetic acid may not be unlikely and this association necessarily implies influence on the course of reactions

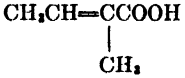
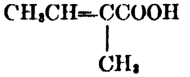
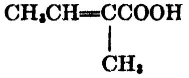
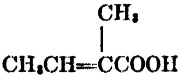
TABLE 7

Effect of temperature on reduced velocity

COMPOUND	REDUCED VELOCITY AT −35°C. (48)	REDUCED VELOCITY AT −78°C. (2)
$H_2C{=}CH_2$	1	1
$C_6H_5CH{=}CH_2$	3.24	3.35
$CH_3CH{=}CH_2$		2.03
$C(CH_3)_2{=}CH_2$	5.5	5.53
$C(CH_3)_2{=}CHCH_3$		10.4
$C(CH_3)_2{=}C(CH_3)_2$	13.6, 14.0	14.0
$CH_2{=}CHCOOH$	0.03	Small
$CH_2{=}CHBr$	0.03	Small
$CH_2{=}CHCHO$		1.5
$CH_3CH{=}CHCHO$		3.0
$CH_3CH{=}CHCOOH$		0.26

TABLE 8

Relative rates of addition of bromine by olefinic compounds

SOLVENT	X	Y	$\frac{k_X}{k_Y}$
Methylene chloride at −78°C. (references 1, 2)	$CH_3CH{=}CH_2$	$CH_2{=}CH_2$	2
	$(CH_3)_2C{=}CH_2$	$CH_3CH{=}CH_2$	2.8
	$(CH_3)_2C{=}CHCH_3$	$(CH_3)_2C{=}CH_2$	1.9
	$(CH_3)_2C{=}C(CH_3)_2$	$(CH_3)_2C{=}CHCH_3$	1.4
	$CH_3CH{=}CHCHO$	$CH_2{=}CHCHO$	2
Acetic acid at 35°C.	 $CH_3CH{=}\underset{\underset{CH_3}{\vert}}{C}COOH$	$CH_3CH{=}CHCOOH$	5.2
Acetic acid at 35°C. (references 3, 4, 5)	$(CH_3)_2C{=}CHCOOH$	 $CH_3CH{=}\underset{\underset{CH_3}{\vert}}{C}COOH$	3.9
Acetic acid at 50°C.	 $CH_3CH{=}\underset{\underset{CH_3}{\vert}}{C}COOH$	$CH_3CH{=}CHCOOH$	3.7
Acetic acid at 50°C.	$(CH_3)_2C{=}CHCOOH$	 $CH_3CH{=}\overset{\overset{CH_3}{\vert}}{C}COOH$	5.5

in this solvent. Until we have adequate evidence to prove the absence of heterogeneity, comparisons of reactions in carbon tetrachloride cannot have much value.

The rôle of catalysts is more difficult to interpret. Investigations have shown that a variety of catalysts (1, 3, 21, 40, 41, 114, 116, 118) is available, and in all cases they are polar compounds that can associate with an olefin or form loose complexes with bromine. The influence of oxygen on these reactions has also to be more fully investigated, though in the case of α,β-unsaturated acids this has been shown to be absent (60, 98).

With these limitations it is possible to draw certain tentative conclusions as to the influence of structure on additive reactivity. For this purpose consider the data presented in table 8.

It is clearly seen that the introduction of an alkyl group has a pronounced activating effect which is cumulative. Other things remaining constant, the symmetry or asymmetry of groups introduced exerts considerable influence. The tables also clearly indicate that before a generalized quantitative interpretation is attempted, we have to know more about the liquid state and about the mutual interaction of groups.

V. REACTIONS BETWEEN OLEFINS AND IODINE

Comparatively little work has been done in this field. Almost the only exhaustive study has been with ethylene and iodine, but even here the photochemical addition reaction does not seem to have been studied in the gaseous state.

Mooney and Ludlam (68) have studied the equilibrium "ethylene + iodine ⇄ ethylene iodide" in the gaseous state between 10° and 65°C., while Arnold and Kistiakowsky (6) have studied the thermal decomposition of ethylene iodide between 200° and 250°C. The former authors find that the kinetics of the reaction can be expressed by the rate equation

$$\frac{\mathrm{d}P}{\mathrm{d}t} = k'P_{\mathrm{EI_2}} - kP_{\mathrm{E}}\cdot P_{\mathrm{I_2}}$$

the intergrated form of which gives

$$k = \frac{1}{t}\,\frac{2.303}{P_{\mathrm{I_2}}}\,\log_{10}\left[\frac{P - P_0}{P - \underline{P}}\right]$$

where P is the equilibrium pressure, P_0 the initial pressure, and $\underline{P}$ the pressure at the time of measurement. Increasing values of k from 1.2×10^{-3} to 4×10^{-3} are obtained and the authors have also evaluated the value of k'. The pressure–time curve clearly indicates an autocatalytic reaction, though dealing with an equilibrium; calculation shows that the curve is not of the $e^{-\phi t}$ type. The authors have also made the interesting observation that the heat of decomposition obtained from the log $K - 1/T$ curve gives a value of 22 kilocalories at 50°C. and 13 kilocalories at 30°C.

The work of Arnold and Kistiakowsky (6) leads to a slightly different reaction-rate equation:

$$\frac{\mathrm{d}[\mathrm{EI_2}]}{\mathrm{d}t} = k[\mathrm{EI_2}] + k'[\mathrm{EI_2}]\,[\mathrm{I_2}]^{1/2}$$

Though it has been suggested that the gaseous decomposition is homogeneous, it is difficult to reconcile this with the observation of these authors that alteration in the surface volume ratio leads to a variation in the velocity constant for decomposition. Considering the reactions with other halogens it is more likely that this is also an essentially heterogeneous reaction in the gas phase. Though experiments on the gas reaction are not many, the reactions in solution, especially in carbon tetrachloride, have been the subject of a fairly complete investigation.

The work of Iredale and Martin (49) indicates a definite period of induction, an initial zero-order reaction followed by a monomolecular reaction and finally by an uncatalyzed bimolecular reaction. Increase of surface or cleaning the reaction vessel with hydrogen fluoride accelerates the reaction, which, however, continues on the same course. It is found that mercury vapor has to be removed if the gas reaction is to be complete. Taking into account all these observations, the following mechanism has been suggested:

(1) $\mathrm{I\ (glass) + C_2H_4I_2 = I{-}I\ (glass) + C_2H_4I}$

(2) $\mathrm{C_2H_4I + C_2H_4I_2 = C_2H_4 + I_2 + C_2H_4I}$

(3) $\mathrm{C_2H_4I = C_2H_4 + I}$

(4) $\mathrm{C_2H_4I_2 + I = C_2H_4I + I_2}$

(5) $\mathrm{C_2H_4 + I = C_2H_4I}$

(6) $\mathrm{I\ (glass) + C_2H_4I = C_2H_4I_2}$

(7) $\mathrm{I\ (glass) + I = I{-}I\ (glass)}$

(8) $\mathrm{I + I_2 = I_3}$

The evidence for the full scheme is, however, inadequate and a further reason for doubt is provided by the author's statement that the results are not reproducible. From a consideration of available experimental evidence Ogg (77) has shown that the reaction is best represented by a chain mechanism rather than the single stage visualized by Arnold and Kistiakowsky (6). Since generally reactions in solution in non-polar solvents like carbon tetrachloride have been found to correspond largely to gas-phase reactions, these results may also be taken to indicate the probable course of gas reaction.

Schumacher and coworkers have shown (100) that the decomposition is sensitized by the photochemical or thermal dissociation of iodine, leading to an experimental rate equation:

$$-\frac{d(\mathrm{C_2H_4I_2})}{dt} = kI_{\mathrm{abs.}}^{1/2}(\mathrm{C_2H_4I_2}) \tag{I}$$

Varying quantum yields indicate a chain mechanism for the reaction, the primary process being dissociation of iodine molecules into atoms, combined with a secondary process, common to the thermal mechanism:

(1) $\mathrm{I_2} + h\nu \rightarrow \mathrm{2I}$

(2,3) $\mathrm{C_2H_4 + I \rightleftharpoons C_2H_4I}$

(4,5) $\mathrm{C_2H_4I + I_2 \rightleftharpoons C_2H_4I_2 + I}$

(6) $\mathrm{I + I\ (+M) \rightarrow I_2(+M)}$

Assuming a constant third body recombination of iodine atoms and a stationary concentration of the free radical C_2H_4I, this chain mechanism leads to a rate equation:

$$-\frac{d(C_2H_4I_2)}{dt} = \frac{k_5 \frac{\phi^{1/2}}{k_6^{1/2}} I_{\text{abs.}}^{1/2}(C_2H_4I_2)}{1 + \frac{k_4(I_2)}{k_3}} - \frac{k_2 \frac{\phi^{1/2}}{k_6^{1/2}} I_{\text{abs.}}^{1/2}(C_2H_4)}{1 + \frac{k_3}{k_4(I_2)}}$$

If the ethylene concentration is small, as in the initial stage of photolysis, the second term of the equation cancels out, while if the denominator of the first term becomes small, it reduces to equation I. The inaccuracy of these simplifying assumptions in the later stages of the reaction and the limitations in the range of stationary concentration in an element of volume lead to the observed deviation of the experimental results from the simplified rate equation.

Mooney and Reid (69) were the first to observe the autocatalytic nature of the reaction in solution and the catalytic influence of free iodine. Their observation that the initial slopes of the curves are proportional to the square root of the iodine concentration is a precursor of the chain mechanism involving iodine atoms. Polissar's (88) work has shown that at temperatures at which the reaction rate is conveniently measurable, the reverse reaction is also facilitated. Having thermal dissociation of iodine as the initial step, Schumacher (99) derived a mechanism analogous to that of Berthoud and Béraneck (*loc. cit.*) for bromine addition, with necessary alterations, taking into account the reversibility of the reaction. Using this mechanism and assuming stationary concentration of C_2H_4I and I

$$(1,6) \quad I_2 \rightleftharpoons 2I$$

$$(2,3) \quad C_2H_4 + I \rightleftharpoons C_2H_4I$$

$$(4,5) \quad C_2H_4I + I_2 \rightleftharpoons C_2H_4I_2 + I$$

he obtained the reaction-velocity equation

$$+\frac{d[C_2H_4I_2]}{dt} = \frac{k_2 K_{I_2}^{1/2}[C_2H_4][I_2]^{1/2}}{1 + \frac{k_3}{k_4[I_2]}} - \frac{k_5 K_{I_2}^{1/2}[C_2H_4I_2][I_2]^{1/2}}{1 + \frac{k_4[I_2]}{k_3}}$$

which, if the term $\frac{k_4}{k_3}(I_2)$ is small or $\frac{k_3}{k_4(I_2)}$ large, simplifies to

$$+\frac{d[C_2H_4I_2]}{dt} = \frac{k_2 k_4 K_{I_2}^{1/2}}{k_3}[C_2H_4][I_2]^{3/2} - k_5 K_{I_2}^{1/2}[C_2H_4I_2][I_2]^{1/2}$$

the actual experimental rate equation obtained by Polissar. Ogg has shown that Kistiakowsky's work in the gas phase also leads to the same result and that Polissar failed to notice the uncatalyzed unimolecular decomposition observed by Arnold and Kistiakowsky (6), presumably owing to its being suppressed at the lower temperatures at which he worked.

Mention may be made also of the careful studies of Forbes and Nelson (31, 32) on the photoiodination of the simpler olefins in chloroform solution at −55°C. The reaction has been found to depend on light intensity and on concentration of the reactants, and the varying quantum yields lead as before to a chain mechanism. They make the significant observation that oxygen is without effect on the quantum yield, and the thermal iodination of the butenes in liquid Freon (CCl_2F_2) was complete within a few minutes even at −150°C.

Robertson (94) and Bythell have studied the addition of iodine to a number of allyl derivatives in nitrobenzene, acetic acid, hexane, and carbon tetrachloride. In the last two solvents, the reaction is found to be heterogeneous, the course of the reaction being generally analogous to the bromine addition.

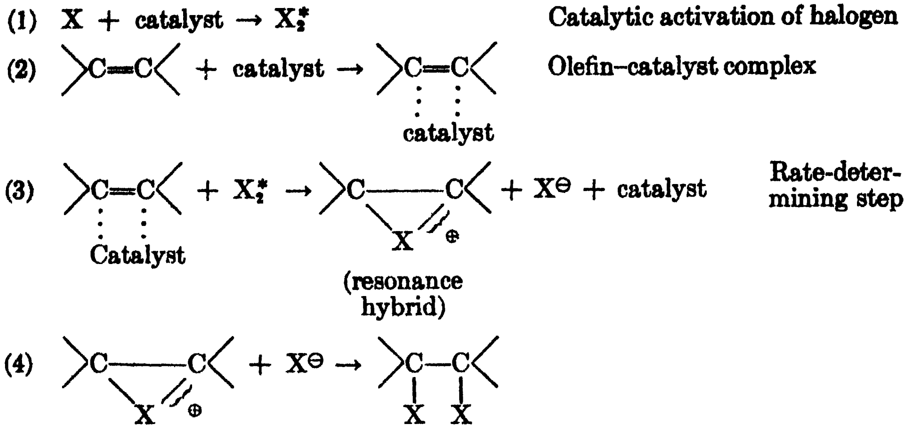
More recently Ghosh and coworkers (18, 19, 34, 35) have studied the addition of iodine to β-amylene and to α-pinene in a number of solvents. In the chain mechanism suggested by these authors for the thermal reaction they postulate the I_6 molecule as taking part in the reaction in preference to smaller polymers. Apart from the work of Groh (38), all studies lead to the existence of only I_2 and I_4 molecules in solution, and the recent magnetic susceptibility studies of Rao and Govindarajan (90) point more to a possible ionization than to the existence of higher polymers of iodine in solution. Further, it is very difficult to accept the view that iodine should behave so differently from the other halogens. The volatility of carbon disulfide and the temperatures used for the experiment, under the conditions stated, preclude any accurate results. The choice of α-pinene is also rather unfortunate, because of a possible Wagner–Meerwein change in the course of the reaction. Doubt is thrown on the results of the photochemical reaction also, when variations in the velocity coefficient of as much as 12 per cent with concentration are found to be neglected.

As yet the olefin–iodine reaction has not received adequate attention in the shape of a systematic study either in polar solvents or for variations in reactivity with systematic structural changes on lines similar to those with bromine.

VI. THE GENERAL MECHANISM OF THE OLEFIN–HALOGEN REACTION

The trend of observations of photochemical and thermal reactions between the different halogens and the carbon–carbon double bond indicates clearly that two different but general mechanisms should explain the course, one for the thermal and the other for the photochemical change. In the case of photochemical reactions, while the essential chain mechanism involves absorption of light quanta by halogens, photoactivation of the olefin cannot be excluded, judging from the photodissociation of olefins. The best general mechanism suggested appears to be that of Leighton (54).

Thermal



The extent to which a catalyst influences the reaction will depend on the degree of activation of the double bond, either thermally or by the presence of activating groups or both. The more the activation by internal factors, i.e., structural influences, the less the influence of external catalytic agents and *vice versa*. The revised scheme suggested can also explain the interconversion of geometrical isomers which depends on whether the reverse reaction, i.e., the rate-determining step in the thermal reaction, or further addition takes place. The formation of a complex with the catalyst accounts also for the varying *PZ* values with systematic changes in structure that indicate the importance of the phase of collision prior to combination. Whether a reaction gives an apparent trimolecular or bimolecular or at times even pseudo-monomolecular constant depends on which of the several steps determines the rate and this is turn depends on the experimental conditions.

The general trend, however, is to indicate that no great difference may be expected among the halogens in this kind of reaction, the behavior of the first member being exceptional on account of its extreme reactivity. Possibly the stability of fluorine as a positive halogen is so small and the ionization energy so different from that of carbon, that the postulated intermediate steps are ruled out, with only a rupture of the olefin leading to a variety of fluorinated products. The others conform to the gradation one might expect from their behavior in other reactions.

It should also be stated that the addition of halogens to olefins is of such a general nature that, irrespective of the substituent groups, the general mechanism should be unaltered, since the reactivity is essentially a function of the polarizability of the double bond. This expectation is confirmed by the observations of Kharasch and Roth on hydrogenation of olefins (reference 44, page 94).

Before concluding, it is interesting to note the variation in the parameters of the Arrhenius reaction-velocity equation with the halogen on the one hand and the structure of the olefin on the other. The energy of activation decreases from chlorine to iodine (101) though, as has been found experimentally, the values of E can be considerably reduced by the presence of activating groups or by catalysts or both. But the significant result is that the probability factor in all the cases turns out to be several powers of ten smaller than the value one might expect theoretically. This brings out clearly that in the formation of a transition state the relative orientation of the reacting olefin and halogen is as important as the frequency of collision on account of the number of degrees of freedom involved, and any adequate interpretation can be possible only after more systematic investigations.

The reactions under discussion present further examples of the apparently simple bimolecular type becoming a complex chain type of reactions.

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COLLEGE GRADUATES WITH TRAINING IN PHYSICS NEEDED FOR WAR RESEARCH AND TEACHING

The heaviest demands for research workers and teachers made upon the Office of Scientific Personnel of the National Research Council are in the field of physics. Now the supply of persons whose chief training has been in this field is exhausted and persons who can do the work of physicists, either in war research or in teaching, must be sought from other fields. There are large numbers of persons in other fields whose scientific and technical training includes sufficient physics for them to do work ordinarily requiring physicists. Several hundred such persons are already substituting for physicists in research and in teaching.

Reports of the National Roster upon the shortages of physicists indicate that several hundred more emergency physicists will be needed. All persons who feel that they may be able to serve in the capacity of physicists, either in research or as teachers of beginning physics in the training programs of the armed forces, should at once communicate with Dr. Homer L. Dodge, Director of the Office of Scientific Personnel, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

ERRATUM

Volume 28, Number 2

Page 226: Footnote 4 should read as follows: "Figure 10 shows that vectors between equivalent points of type 3 occur relatively infrequently and so might reasonably be associated with the small relative maximum which does occur in the Patterson Harker section at $z = 0$. I do not therefore consider that this point arrangement is entirely excluded by the criticism made by Langmuir and Wrinch (Proc. Phys. Soc. (London) 51, 617 (1939))."

The author very much regrets her original misstatement.

THERMAL ANALYSIS OF LIQUEFIED GASES

HAROLD SIMMONS BOOTH AND DONALD RAY MARTIN

Morley Chemical Laboratory, Western Reserve University, Cleveland, Ohio

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CONTENTS

I. Introduction 57
II. Generation, purification, and storage of gases 59
  A. Generation 59
  B. Purification 59
  C. Storage 60
III. Experimental methods for the establishment of gaseous mole fractions 61
  A. Synthetic volumetric methods 61
  B. Synthetic gravimetric methods 63
IV. Experimental methods for the determination of freezing points 63
V. Possible sources of error in thermal analysis of liquefied gases 66
  A. Errors in the determination of mole fractions 66
    1. Pressure measurements 66
    2. Volume measurements 68
    3. Calibrated-flask temperature 68
    4. Connecting manifold 68
    5. Compressibility coefficient 68
  B. Errors in the determination of freezing points 68
    1. Freezing-point cell diameter 68
    2. Thermocouple 68
      (a) Type 68
      (b) Calibration 69
      (c) Immersion depth 69
      (d) Closeness to bottom of cell 69
    3. Recording potentiometer 69
    4. Cooling rate 69
    5. Viscosity 69
VI. Systems reported in the literature 69
VII. Summary 87

I. INTRODUCTION

Thermal analysis of liquefied gases is based upon the experimental determination of the transition points of the cooling curves of given mixtures of two liquefied gaseous components in various known proportions. These transition temperatures are plotted *versus* the concentrations expressed in mole fractions to give a temperature–concentration phase-rule diagram.

A cooling curve is obtained by plotting the temperature *versus* the time when a two-component liquid system is caused to cool slowly to a temperature below its freezing point. As long as the system consists of a single liquid phase, the cooling curve will remain smooth and continuous. If a second phase appears, a sudden discontinuity in the curve will occur. If the new phase has the same composition as the liquid phase, the temperature will remain constant until all of the liquid phase has disappeared. If the new phase has a different composi-

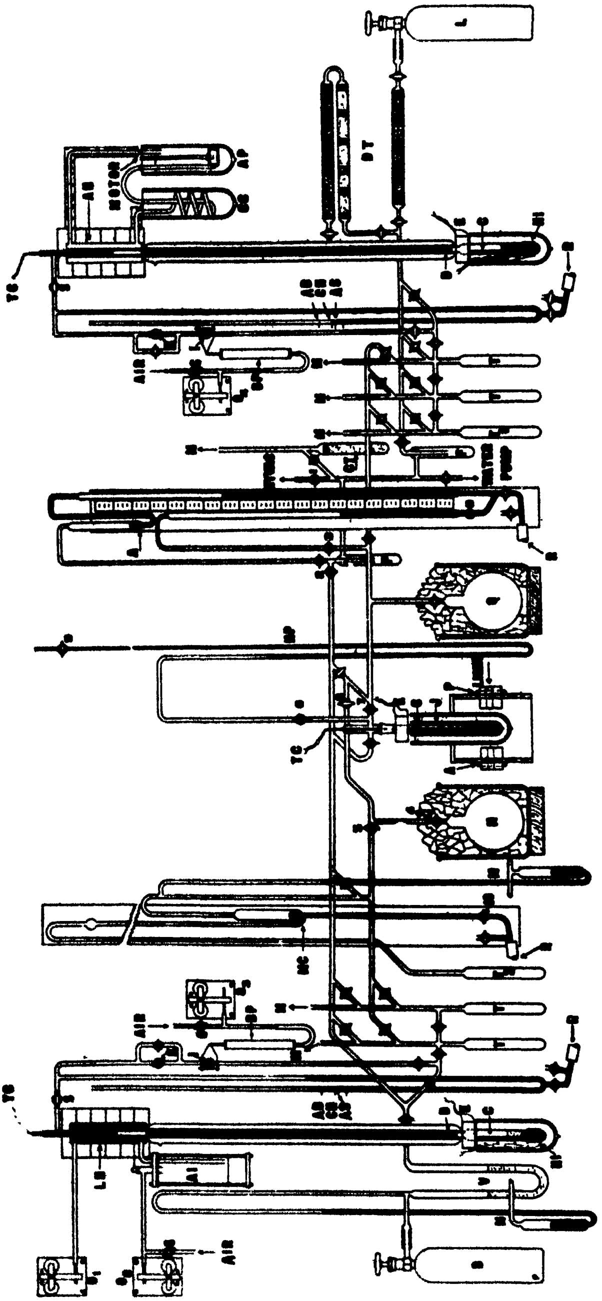

FIG. 1. Typical apparatus used for thermal analysis of liquefied gases

tion from the liquid phase, the cooling curve will undergo a change of slope due to the continuous alteration of the composition of the liquid phase as the temperature drops. Should a third phase form, the temperature of the system will remain constant until one of the phases has completely disappeared, and then give a second break in the cooling curve.

If the temperatures at which the transition begins on the cooling curves for various concentrations of the two components are plotted *versus* the concentration expressed in mole fractions or mole per cents, a temperature–concentration phase-rule diagram results.

In a temperature–concentration phase-rule diagram a compound displays a maximum, with a minimum usually occurring on each side of the maximum. This minimum temperature is usually called the eutectic point and represents the lowest temperature of freezing obtainable in any given system. This eutectic point will occur reproducibly at a definite concentration of the two components of the system in question and represents the freezing point not of a compound but of a mixture.

A compound can also be detected by the character of the cooling curve of a specific composition. A compound during freezing maintains a constant temperature, owing to the fact that the solid and liquid phases have the same composition. A liquid mixture when freezing merely gives a continuous change in the slope of the cooling curve, unless an enantiotropic transition takes place. Since such transitions proceed with accompanying energy changes, a discontinuity in the curve would occur.

The purpose of this paper is to make a critical survey of the investigations which have been published on the thermal analysis of liquefied gases, to correlate and evaluate the methods used, and to describe the binary systems reported.

In the thermal analysis of a gaseous system provision must be made in the apparatus for (*a*) the generation, purification, and storage of the gaseous components, (*b*) the establishment of the mole fractions, and (*c*) the determination of the freezing point of the mixture corresponding to these mole fractions. A typical apparatus for a thermal analysis is shown in figure 1 (17).

II. Generation, Purification, and Storage of Gases

A. GENERATION

It is desirable for the sake of convenience to obtain the gases to be used in a thermal analysis from cylinders. However, frequently this is not possible and it is necessary to generate the desired gas in the laboratory. The method of generation depends upon the gas desired, and generally consists in mixing the reactants in a generator flask attached to the bottom of a scrubbing tower. The gaseous products are taken off the top of the tower, led through a series of traps to condense the undesirable products, and condensed in the still pot of a fractionating column where further purification takes place (16).

B. PURIFICATION

The purity of the gases used is a primary prerequisite to a thermal analysis, because a slight trace of an impurity changes the freezing point of the pure is now evacuated to the vapor pressure of the pure gas at liquid-air temperature. Flask H now contains a known volume of the gaseous component under a known pressure P', at a known temperature 0°C. The flask stopcock 4 is then opened slightly and the desired amount of gas distilled into the freezing-point cell by opening stopcock 7. When the desired amount of the gas has been condensed, as indicated by the pressure drop on the manometer O, stopcock 7 is again closed. When equilibrium has been attained, the pressure P'' of the remaining gas in the calibrated flask H is read and recorded. Stopcock 4 on flask H is slowly closed and the gas in the manifold condensed into the freezing-point cell by opening stopcock 7. When all of the gas is condensed out of the manifold into the freezing-point cell, stopcock 7 is closed. Each time an increment of gas is added to the freezing-point cell, the above procedure has to be repeated.

Ruhemann and Lichter (37) used the same principle with a calibrated copper bomb and a baro-manometer in their study of the system nitrogen–oxygen.

The weight of the gas condensed in the freezing-point cell can then be calculated. The weight m of a gas of density L, at 0°C. and under a pressure p, in the volume in liters of the calibrated flask V, is given by the equation

$$m \quad \frac{pV}{760} L\left(1 + \frac{p - 760}{760} A_0^1\right)$$

where A_0^1 represents the compressibility of the gas between zero and 1 atmosphere. The pressure p in the equation is equal to the difference in the pressure readings before and after some of the gas is condensed from the calibrated flask into the freezing-point cell.

Germann and Booth (25) have modified the above equation to

$$W \quad \frac{LV(P' - P'')}{(1000)(760)} = \frac{LVP^0}{(1000)(760)}$$

in which W is the weight of the gas condensed, P' is the pressure of the gas in the flask initially, and P'' is the pressure in the flask after condensation of some gas into the freezing-point cell, V is the volume of the calibrated flask in milliliters, and P^0 is the change in pressure caused by the condensation of some of the gas into the freezing-point cell. The molecular composition is desired instead of the weight, and according to the perfect gas law,

$$\frac{M_1}{M_2} = c\frac{P_1^0}{P_2^0}$$

in which M_1 and M_2 are the number of moles of gas 1 and of gas 2, P_1^0 and P_2^0 are their pressures, and c is the ratio of the volumes of the two calibrated flasks in which each of the gases was measured.

This equation, when corrected for the deviation of the two gases from the perfect gas law, becomes

$$\frac{M_1}{M_2} = c\,\frac{P_1^0 + \frac{P_1^0}{760} A_1']_0^1}{P_2^0 + \frac{P_2^0}{760} A_2']_0^1} = c\,\frac{P_1^0(760 + A_1']_0^1)}{P_2^0(760 + A_2']_0^1)}$$

in which $A'_1]_0^I$ and $A'_2]_0^I$ are the compressibilities of the respective gases between zero and 1 atmosphere. The mole fraction N_1 of gas 1 is given by the expression

$$N_1 = \frac{M_1}{M_1 + M_2} = \frac{cP_1^0(760 + A'_1]_0^I)}{cP_1^0(760 + A'_1]_0^I + P_2^0(760^p + A'_2]_0^I)}$$

The corrective factors are small and may be neglected in most cases, especially if the gases are in approximately corresponding states at 0°C. and 1 atmosphere. In this case the calculation takes the simple form

$$N_1 = \frac{M_1}{M_1 + M_2} = \frac{cP_1^0}{cP_1^0 + P_2^0}$$

Another volumetric method which has been used is the measurement of the gases by a gas buret. Scheflan and McCrosky (40) measured each of the gaseous components in separate gas burets with mercury as the retaining fluid. Wheat and Browne (46) used water-jacketed gas burets for each of their components, with mercury as the retaining fluid for methyl chloride and a saturated sodium chloride solution as the retaining liquid for chlorine. Booth and Willson (18) have found that increased accuracy can be obtained by using a double baroburet.

Bagster (1) used a graduated ampule as a liquid buret. By distilling out a given volume of gas and recording the change in volume of the liquefied gas in the calibrated ampule, he calculated the mole fractions from the liquid densities of the gases. Corrections were not made for the change in volume of the ampule with temperature, thus introducing some error. This method would be advantageous with gases which attack mercury. Biltz and Bräutigam (15) used a similar method.

B. SYNTHETIC GRAVIMETRIC METHODS

Gravimetric methods have not been as widely used as volumetric methods in the synthetic establishment of the composition of mixtures in the thermal analysis of liquefied gases, probably owing to the fact that volumetric methods are more convenient to use with gases.

van der Goot (27), working with the system chlorine–sulfur dioxide, condensed one component into a weighed reaction tube, sealed the tube, and weighed it. The tube was then opened, the other component added, and the tube resealed and reweighed. All weighings were made at the same temperature. By this method the mole per cent of the mixture was determined to ±0.1 per cent when approximately equal amounts of the two components were added. With an excess of either component the accuracy was less.

IV. Experimental Methods for the Determination of Freezing Points

After the mixture of the two components has been made and its concentration in mole per cent is known, the cooling curve for the mixture must be determined in order to develop the temperature–concentration phase-rule diagram. The early workers in the field had to determine their cooling curves manually by periodically reading the temperature of their thermometers or thermocouples and recording these temperatures and time intervals. Then it was necessary for them to plot the temperature *versus* the time in order to determine where their cooling curve changed slope or gave an abrupt break. This laborious and inaccurate method has now been superseded by the use of thermocouples with recording potentiometers.

The basic procedure for the determination of freezing points was established by Beckmann (14). He used a thermometer and magnetically operated vertical stirrer inside the freezing-point cell. The magnetic stirrer consisted of a metal ring held horizontally above another metal ring by platinum wire and connected to a top iron ring coated with platinum. His freezing-point cell was surrounded by a solenoid. When the electric current was intermittently applied, the stirrer rose and dropped in the freezing-point cell, thus stirring the liquid. The freezing-point cell was then immersed in a suitable refrigerating bath the temperature of which could be controlled. Agitation of the bath insured uniform cooling.

Baume (3) modified the apparatus by placing the magnetic stirrer of the Beckmann apparatus within the freezing-point cell. The stirrer used differed from Beckmann's metallic stirrer, being all glass with a piece of iron enclosed in the uppermost glass ring. A pentane thermometer which had to be calibrated for errors due to stem emergence was used. To obtain a slower rate of cooling Baume surrounded the freezing-point cell with a glass jacket, thus creating a dead air space between the cell and the liquid-air bath. To prevent the jacket from frosting and thus hindering vision of the cell, he put anhydrous calcium chloride within the jacket. However, experience has shown that this is not effective in preventing frosting.

Bagster (1) improved the procedure by controlling the rate of cooling by means of a petroleum ether bath which was cooled by liquid-air injections and was stirred by dry air.

Germann and Booth (25) increased the stirring efficiency of Baume's apparatus by using a glass-spiral stirrer with a piece of soft iron sealed inside the top of the stem. The vertical motion of the stirrer gave the liquid a swirling motion.

Coffin and Maass (21) recorded the temperature of the liquid-air-cooled petroleum ether bath in which the mixture in the freezing-point cell froze, by means of a platinum resistance thermometer in the bath. It has been the authors' experience that resistance thermometers are too slow in attaining equilibrium for use in the observation of freezing points.

Biltz and Bräutigam (15) used a stirrer of the Beckmann type and determined the freezing points by use of an aluminum-block thermostat. The block was divided into two halves, separated by a very narrow air space. A recess in one half was charged with liquid air as required to give the desired cooling rate. Two holes were drilled in the other half; one for a pentane thermometer to record the temperature of the block, and the other hole for the freezing-point cell. The cell had a glass inner tube, surrounded by a stirrer, which contained a fused-quartz resistance thermometer. Measurements were reported accurate to ±0.5°C.

Booth and Willson (18) improved the technic of Baume by means of three modifications: (*1*) Polarized light was used to establish the moment at which crystals first formed in the liquid mixture. The cell was placed between two polaroid discs so that a beam of polarized light passed through the liquid in the cell, with the result that the microscopic anisotropic crystals flashed as white particles in a dark field before they were visible to the unaided eye (see figure 2).

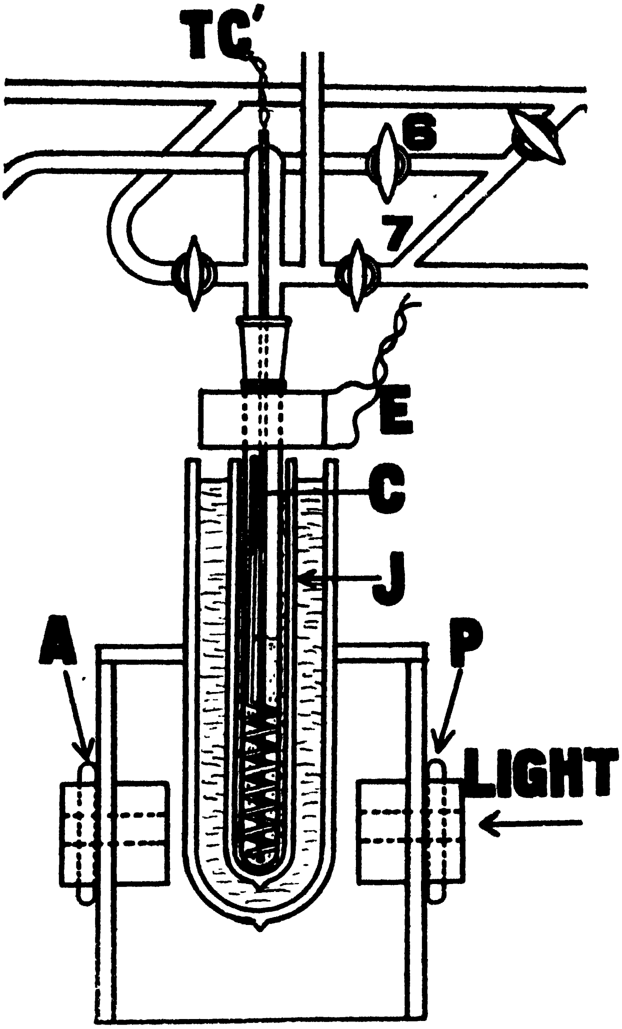

FIG. 2. The freezing-point cell

(*2*) The freezing point was recorded instantly in two ways on the chart of a Leeds and Northrup Micromax recording potentiometer connected to the multijunction copper-constantan thermocouple in the freezing-point cell. A manually actuated electromagnetic pen indicated on the cooling-curve chart the time at which the crystals were first seen, and then the change of slope in the cooling curve itself indicated the freezing point. However, in the vicinity of a eutectic the transition point is difficult to establish accurately by means of a cooling curve only. The use of polarized light and a magnetic pen enables the experimenter to establish transition points definitely at all compositions. (*3*) A vacuum jacket was used around the freezing-point cell.

In the method adopted in this laboratory the freezing-point apparatus shown in figure 2 (17) is used. The freezing-point cell contains a thin-walled glass thermocouple well TC, surrounded by an all-glass spiral stirrer with a piece of iron sealed in the top of its stem C. The stirrer is actuated by solenoid E. The rate of cooling is controlled by the small Dewar flask J, which is immersed in a quart Dewar flask containing liquid air. The quart Dewar flask is surrounded by a light-proof box through which passes a beam of light. The light passes through polarizer P and the freezing-point cell is observed through analyzer A.

The above methods are commonly employed for the determination of freezing points in the thermal analysis of liquefied gases. Two other methods have been reported: (*1*) The freezing points of mixtures of hydrogen chloride and nitric oxide were determined by use of a thermocouple in a conductivity cell (35). The freezing point was detected visually and checked when the conductivity dropped to zero. Difficulty was experienced in this method when the mole fraction approached 0.5, as both components tended to condense separately as pure solid phases. (*2*) Ruhemann and Lichter (37) determined freezing points in a vacuum calorimeter.

V. Possible Sources of Error in Thermal Analysis of Liquefied Gases

A discussion of the possible sources of error in the modified Baume method of thermal analysis of liquefied gases, now most generally used, is pertinent.

A. ERRORS IN THE DETERMINATION OF MOLE FRACTIONS

1. Pressure measurements

A great many specialized manometers have been built in an effort to eliminate the errors to which this instrument is subject, chief of which are the residual pressure in the barometric vacuum and the variations in the meniscus. Both objections would appear to be remedied in a barometer of wide bore, the vacuum chamber of which communicates with a vacuum pump; here capillarity no longer exercises an appreciable influence, the meniscus remaining perfectly flat except at the edges, and the quality of vacuum is under the experimenter's direct observation and control. Experience with this type of barometer has shown its superiority over the type composed of narrow glass tubing (23).

All pressure measurements are made, therefore, by a special U-type manometer, having a vacuum on one side which is established by a trap after the manner of the Germann manometer (23) (see A, figure 1). Both arms of the barometer are made of tubing of the same diameter. In this laboratory tubing of 14-mm. inside diameter has been found satisfactory. The manometer is filled by closing stopcock O and by opening stopcocks 2 and 3 (see figure 1). Both arms of the manometer are then evacuated, after which the mercury reservoir is raised until the mercury in the right arm rises in the capillary tubing. The reservoir is then lowered until the mercury level is at the base of the barometer. This operation is repeated slowly about twelve times to insure that no air will be trapped within the barometer. Then the mercury reservoir is raised until a small quantity of mercury has gone over into the trap A. Subsequent lowering of the mercury reservoir causes the mercury column to break in the capillary tubing, thus creating a vacuum over the mercury in the right arm. This lowering and raising of the mercury and subsequent overflow into A is repeated until no bubble is driven over. Stopcock O is then opened and stopcock 2 closed and the barometer is ready for use.

Since, in reading the absolute barometer, accuracy is required only to 0.5 mm., corrections for error due to capillary depression, for the thermal expansion of mercury and of glass, and for gravity become negligible.

When a gas in a calibrated flask is completely condensed into the freezing-point cell, a pressure change of about 760 mm. takes place. The pressure reading is easily accurate to 1 part in 760. The ratio of the volume of the calibrated flask to the volume of the freezing-point cell is usually such that the calibrated flask must be emptied twice in order to have sufficient liquefied gas in the freezing-point cell to give a reliable freezing point. The accuracy of the readings of the pressures is the limiting factor in the accuracy of determining the mole fractions because

$$N_1 = \frac{M_1}{M_1 + M_2} \qquad \frac{cP_1^0}{cP_1^0 + P_2^0}$$

Assuming that the calibrated flask must be emptied twice to supply sufficient liquefied gas for a freezing point, the accuracy of the pressure readings for this component is 2 parts in 1520. The second component is then added in sufficient quantity to produce the desired mole fraction. If a pressure reduction of 100 mm. on the gas in the calibrated flask is assumed sufficient to introduce the desired quantity of the second component, the following calculation shows the accuracy of the mole fraction thus established:

$$N_1 = \frac{1520 \pm 2}{(1520 \pm 2) + (100 \pm 1)} = \frac{1520 \pm 2}{1620 \pm 3} = 0.938$$

The error is 3 parts in 1620, or 1 part in 540, and is equivalent to 0.2 per cent. The following table shows how the accuracy increases as succeeding increments of the second component are added until the flask is emptied. When a second flask full of the second component is required, the accuracy again drops.

P_1^0	P_2^0	N_1	ERROR IS 1 PART IN
mm.	*mm.*		
1520 ±2	100 ±1	0.938	540
1520 ±2	200 ±1	0.884	573
1520 ±2	760 ±1	0.667	760
1520 ±2	860 ±2	0.639	595
1520 ±2	1520 ±2	0.500	760

The greatest accuracy which can be claimed for mole fractions established by this procedure is 1 part in 500. The accuracy could be greatly increased by using a glass scale on the barometer in conjunction with a cathetometer, but such accuracy is not necessary for this purpose.

2. Volume measurements

The volume of the calibrated flasks is accurate to at least 1 part in 25,000 for 1-liter flasks. The method used for their calibration is that used by Germann and Booth (24).

3. Calibrated-flask temperature

The calibrated flasks are kept completely covered up to the stopcocks with cracked ice to insure that their temperatures are at 0°C.

4. Connecting manifold

The vapor pressure of the solidified gas in the freezing-point cell at liquid-air temperature results in a definite amount of the gas remaining in the connecting manifold. However, after each pressure reading the gas in the manifold is condensed into the freezing-point cell. Since the amount of gas left after this condensation is known from the vapor pressure of the gas at liquid-air temperature, condensation should be continued until the barometer reads this pressure. After the two gases are mixed, condensation must be continued until no further pressure change is noted on the absolute barometer per given time interval.

5. Compressibility coefficient

The coefficients of compressibility, $A_1]_0^{l}$ of some of the gases which have been used in thermal analysis investigations are not known. Any error introduced by not using these coefficients is negligible if the gases deviate only slightly from the perfect gas law or if the coefficients for the two gases are almost the same when the gases are in corresponding states.

B. ERRORS IN THE DETERMINATION OF FREEZING POINTS

1. Freezing-point cell diameter

Booth and Martin (17) found that the diameter of the freezing-point cell had no effect upon the freezing point obtained provided the thermocouple was sufficiently immersed. A cell having an outside diameter of 14 mm. proved to be the most practical.

2. Thermocouple

(*a*) *Type:* The copper–constantan thermocouple is used because it gives more millivolts per degree than other commonly used thermocouples (except iron–constantan), and because its calibration curve for liquid-air temperatures is better known (30).

Fine silk-covered 32-gauge wire is used to prevent error due to conduction of outside heat to the junction. The junctions should be silver-soldered and arranged in the well above one another to prevent short-circuiting.

(*b*) *Calibration:* The thermocouple is usually calibrated against a platinum resistance thermometer in baths of melting ice, carbon dioxide snow, and liquid air. The actual values are then plotted parallel to the theoretical values (28), and this calibration curve is used to establish all experimentally determined temperatures. In the absence of a resistance thermometer the deviation can be established with satisfactory accuracy by the use of fixed points (43).

(*c*) *Immersion depth:* Booth and Martin (17) found that the top junction of a multijunction thermocouple should be immersed at least 4 cm. to give reliable freezing-point data at temperatures around −100°C.

(*d*) *Closeness to bottom of cell:* It was found that the distance of the bottom of the thermocouple from the bottom of the freezing-point cell had no effect upon the recorded temperature of the freezing point, provided the thermocouple was sufficiently immersed (17).

3. Recording potentiometer

A Leeds and Northrup Micromax recording potentiometer automatically records the cooling curve. It is accurate to 0.3 per cent of the millivoltage range. The recording potentiometers used in this laboratory have a range of 10 millivolts (0–10 and 5–15 millivolt ranges) and therefore are accurate to 0.03 millivolt. The recorder charts can be read to 0.02 millivolt. An optimum rate for the speed of the chart paper through the recorder is 8 in. per hour when the recorder is balancing every second and when the cooling rate is around 4°C. min.^{-1} (17).

4. Cooling rate

By use of a partially exhausted Dewar-type container for the freezing-point cell (J in figure 2), it was possible to maintain an optimum cooling rate of 3 to 3.5°C. per minute (17).

5. Viscosity

Later in the discussion of the various systems which have been studied by thermal analysis it will be noticed that sections of some of the phase-rule diagrams could not be determined, owing to high viscosity and to glass formation.

VI. SYSTEMS REPORTED IN THE LITERATURE

Only the binary systems of liquefied gases studied by thermal analysis in which *both* components are gases under standard conditions will be considered. In some of the systems a pressure in excess of 1 atmosphere has been created within the system, owing to the vapor pressures of the components. Only the salient data about each system will be given.

The method of classification is alphabetical. The components of each system are arranged alphabetically, as are also the systems. For example, the system composed of sulfur dioxide and boron trifluoride is listed as boron trifluoride–sulfur dioxide.

1. Acetylene–hydrogen bromide (32)

Acetylene, f.p. −81.8°C.; hydrogen bromide, f.p. −86.0°C. A eutectic occurred at 34.4 mole per cent acetylene and −126°C. No compounds were found. (See figure 3.)

2. Acetylene–methyl ether (8)

Acetylene, f.p. −81.5°C.; methyl ether, f.p. −138.0°C. Eutectics occurred at 64.5 mole per cent acetylene and −121.0°C., and at 19 mole per cent acetylene and −152.0°C. The compound $C_2H_2 \cdot (CH_3)_2O$, f.p. −117.4°C., was formed. The diagram is incomplete between 80 and 100 mole per cent acetylene. (See figure 4.)

3. Allylene–hydrogen bromide (33)

Allylene, f.p. −105.0°C; hydrogen bromide, f.p. −86.0°C. Eutectics occurred at approximately 63 mole per cent allylene and −132°C., and at approximately 24.5 mole per cent allylene and −138°C. The compound $C_3H_4 \cdot HBr$, f.p. approximately −126°C., was formed. (See figure 5.)

4. Ammonia–hydrogen sulfide (40)

Ammonia, f.p. −78°C.; hydrogen sulfide, f.p. −83.5°C. Eutectics occurred at 95 mole per cent ammonia and −88°C., and at 75 mole per cent ammonia and −18°C. The compounds NH_4HS, f.p. +118°C., and $(NH_4)_2S$ were formed. The diagram was incomplete. (See figure 6.)

5. Ammonia–methyl ether (11, 13)

Ammonia, f.p. −78.3°C.; methyl ether, f.p. −137.6°C. Eutectics occurred at 62.5 mole per cent ammonia and −91.3°C., and at 5 mole per cent ammonia and −141.1°C. The compound $NH_3 \cdot (CH_3)_2O$, f.p. −89.3°C., was formed. (See figure 7.)

6. Argon–boron trifluoride (18)

Argon, freezing point not given; boron trifluoride, f.p. −127°C. Pressure–temperature diagrams for various mole fractions were determined, and from these data a temperature–concentration phase-rule diagram was made of the stabilized system by extrapolation of the temperature upward to a pressure sufficiently high to be above the decomposition pressure for all of the compounds found. Data were given for the compounds $A \cdot BF_3$, f.p. −128.6°C.; $A \cdot 2BF_3$, f.p. −127.6°C.; $A \cdot 3BF_3$, f.p. −128.3°C.; $A \cdot 6BF_3$, f.p. −128.3°C.; $A \cdot 8BF_3$, f.p. −128.4°C.; and $A \cdot 16BF_3$. Data were given for eutectics at 19.9 mole per cent argon and −129.7°C., and at 30.0 mole per cent argon and −131.6°C. The phase-rule diagram shows eutectics at approximately 1.5, 8, 13, and 38.5 mole per cent argon. (See figure 8.)

7. Argon–krypton (44)

Argon, f.p. approximately −189°C.; krypton, f.p. approximately −157°C. Non-porous mixed crystals were formed. A smooth S-shaped curve was obtained. (See figure 9.)

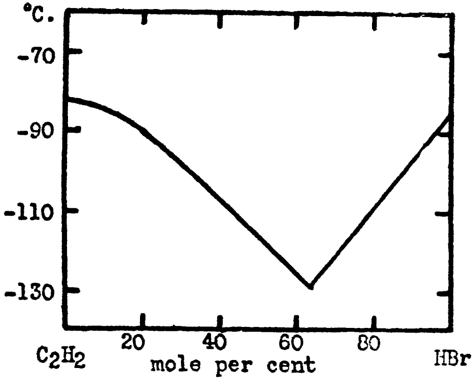

FIG. 3. Acetylene-hydrogen bromide system

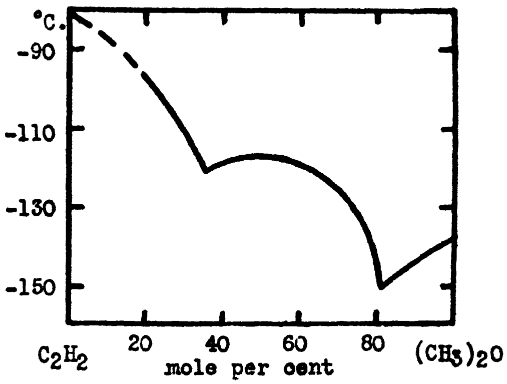

FIG. 4. Acetylene-methyl ether system

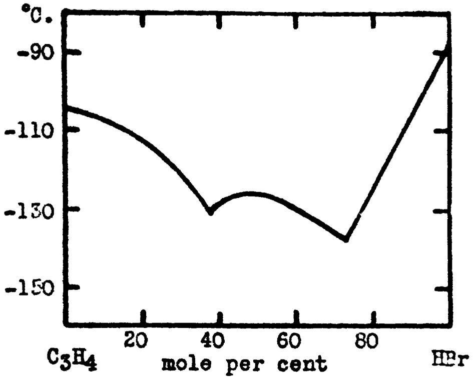

FIG. 5. Allylene-hydrogen bromide system

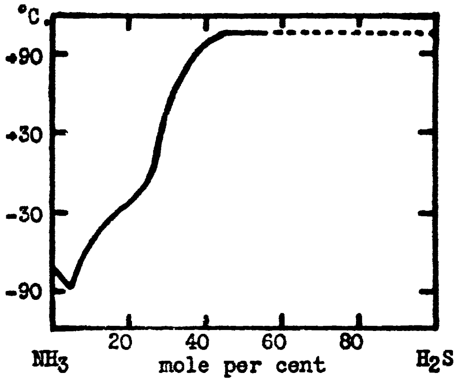

FIG. 6. Ammonia-hydrogen sulfide system

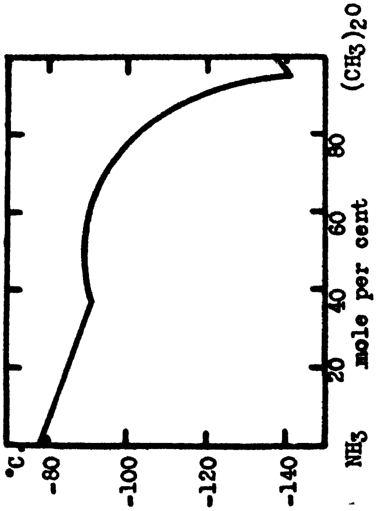

FIG. 7. Ammonia-methyl ether system

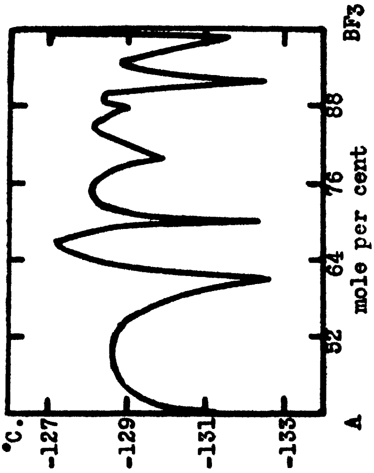

FIG 8. Argon-boron trifluoride system

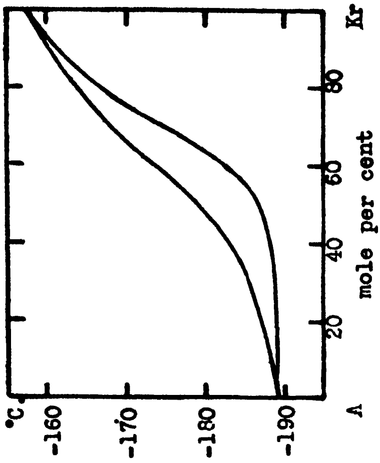

FIG. 9. Argon-krypton system

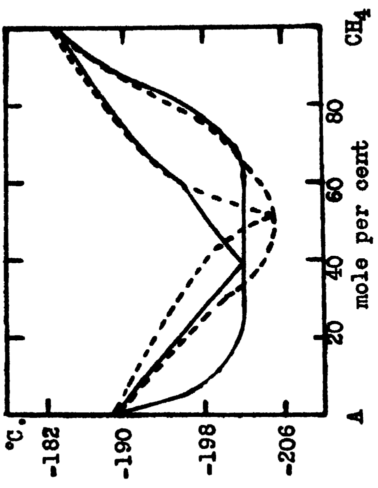

FIG. 10. Argon-methane system

8. *Argon–methane (22, 44)*

Argon, f.p. −189.0°C.; methane, f.p. −183.1°C. The point of equal concentrations lies around 60 mole per cent argon, and −201.9°C. (22). (See the solid-line curve in figure 10.)

Argon, f.p. approximately −189°C.; methane, f.p. approximately −182.4°C. Non-porous mixed crystals were formed with a point of equal concentrations at approximately 48 mole per cent argon and −205.4°C. (44). (See the broken-line curve in figure 10.)

9. *Argon–nitrogen (22, 36)*

Argon, f.p. −189.0°C.; nitrogen, f.p. −210.0°C. Solid solutions were formed (22). (See figure 11.)

10. *Argon–oxygen (22, 36, 44)*

Argon, f.p. −189.0°C.; oxygen, f.p. −219.0°C. Peritectic point occurred at about 20 mole per cent argon and −218.1°C. (22). (See the solid-line curve in figure 12.)

Ruhemann (36) reported this system as a degenerate peritectic type. The original reference was not available, so no data were obtained.

Argon, f.p. approximately −189°C.; oxygen, f.p. −218.9°C. A miscibility gap exists between 10 and 21 mole per cent argon with the peritectic point occurring at 10 mole per cent argon and −217.3°C. (44) (See the broken-line curve in figure 12.)

Veith and Schröder (44) reported that their data agreed with those of Ruhemann (36) fairly well on the argon side but that on the oxygen side there was a discrepancy in the vicinity of the peritectic point.

11. *Boron trifluoride–hydrogen chloride (17)*

Boron trifluoride, f.p. −127.0°C.; hydrogen chloride, f.p. −113.1°C. A eutectic occurred at 72.3 mole per cent boron trifluoride and −134.15°C. No compounds were reported. (See figure 13.)

12. *Boron trifluoride–hydrogen sulfide (25)*

Boron trifluoride, f.p. −128.5°C.; hydrogen sulfide, f.p. −82.0°C. Eutectics occurred at 78 mole per cent boron trifluoride and −147.5°C., and at 53 mole per cent boron trifluoride and −137°C. The compounds $BF_3 \cdot H_2S$, f.p. −140°C., and $BF_3 \cdot 7H_2S$, f.p. −99°C., were found. (See figure 14.)

13. *Boron trifluoride–methyl chloride (17, 20, 26)*

Boron trifluoride, f.p. −118.5°C.; methyl chloride, f.p. −88.5°C. Maxima were reported for 33 mole per cent boron trifluoride and 15 mole per cent boron trifluoride. The suggestion was made that the methyl chloride was contaminated with methyl ether (26).

Boron trifluoride, f.p. −112°C.; methyl chloride, f.p. −78°C. This analysis was made with especially purified methyl chloride. A eutectic occurred at

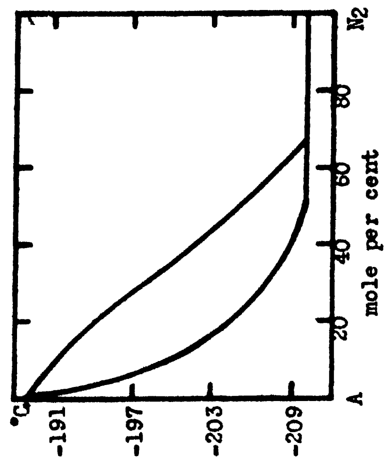

FIG. 11. Argon-nitrogen system

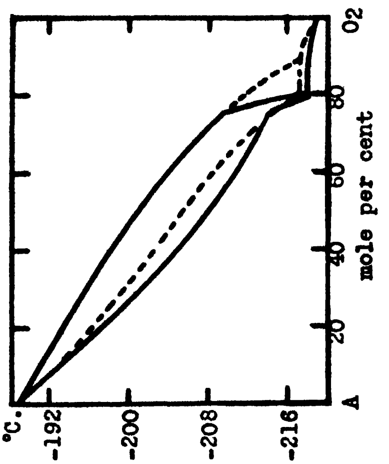

FIG. 12. Argon-oxygen system

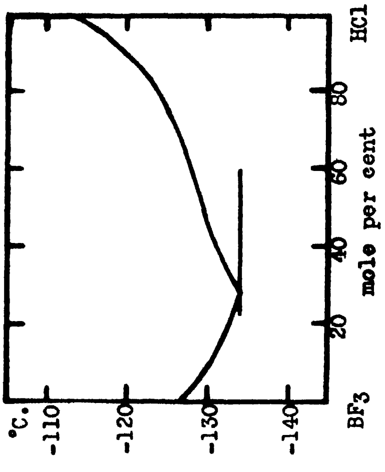

FIG. 13. Boron trifluoride-hydrogen chloride system

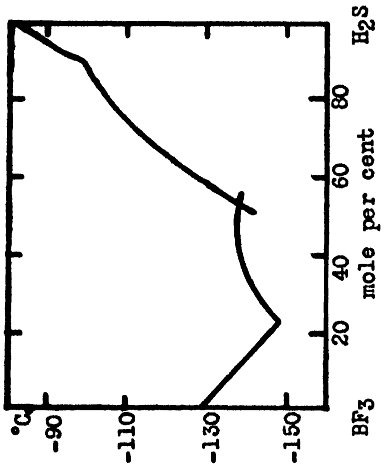

FIG. 14. Boron trifluoride-hydrogen sulfide system

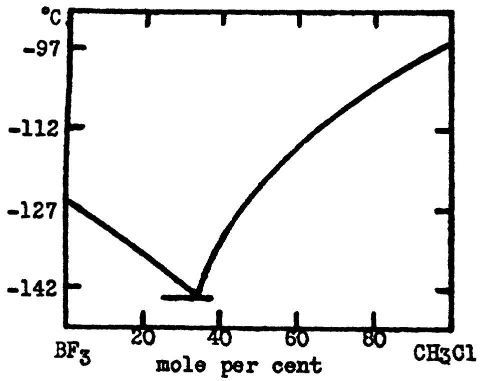

FIG. 15. Boron trifluoride–methyl chloride system

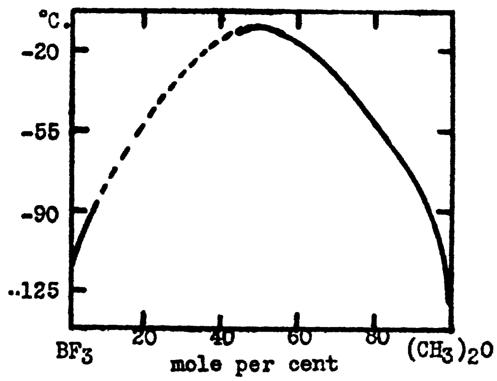

FIG. 16. Boron trifluoride–methyl ether system

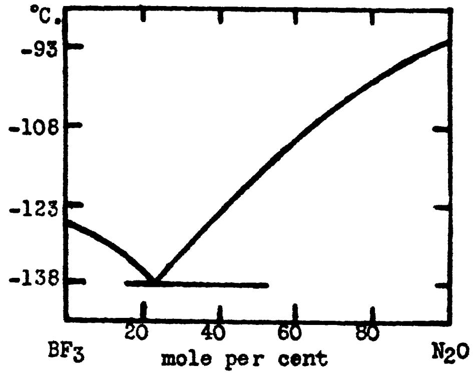

FIG. 17. Boron trifluoride–nitrous oxide system

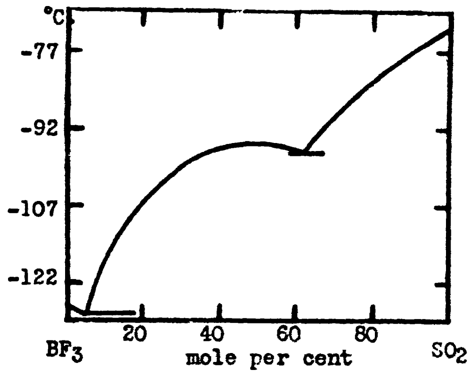

FIG. 18. Boron trifluoride–sulfur dioxide system

70 mole per cent boron trifluoride and −137°C. All temperatures were high, owing to the use of a pentane thermometer which was not corrected for stem emergence (20).

Boron trifluoride, f.p. −126.7°C.; methyl chloride, f.p. −96.65°C. A eutectic occurred at 65.5 mole per cent boron trifluoride and −144.8°C. No compounds were reported. (See figure 15 (17).)

14. Boron trifluoride–methyl ether (20, 26)

Boron trifluoride, f.p. −118.5°C.; methyl ether, f.p. −130.5°C. The compound $BF_3 \cdot (CH_3)_2O$, f.p. approximately −10°C., was reported. The curve was incomplete, owing to excessive pressure on the boron trifluoride side, but it seemed to indicate a second compound between 60 and 90 mole per cent boron trifluoride. The temperatures were high, owing to the use of a propane thermometer without correction for stem emergence. (See figure 16.)

15. Boron trifluoride–nitrous oxide (17)

Boron trifluoride, f.p. −126.8°C.; nitrous oxide, f.p. −91.05°C. A eutectic occurred at 76.6 mole per cent boron trifluoride and −138.0°C. No compounds were reported. (See figure 17.)

16. Boron trifluoride–sulfur dioxide (17)

Boron trifluoride, f.p. −126.75°C.; sulfur dioxide, f.p. −73.5°C. Eutectics occurred at 38.0 mole per cent boron trifluoride and −97.15°C., and at 95.2 mole per cent boron trifluoride and −128.6°C. The compound $BF_3 \cdot SO_2$, f.p. −96.0°C., was found. (See figure 18.)

17. Butylene–hydrogen chloride (21)

β-Butylene, f.p. −127°C.; hydrogen chloride, f.p. −112°C. The diagram is incomplete with more than 67 mole per cent of β-butylene present.

The α-butylene–hydrogen chloride system was run only between 0 and 25 mole per cent α-butylene, because mixtures with more than 25 mole per cent α-butylene were liquids at liquid-air temperatures. (See figure 19.)

18. Carbon dioxide–methyl ether (12, 13)

Carbon dioxide, f.p. −56.7°C.; methyl ether, f.p. −137.6°C. A eutectic occurred at 22.5 mole per cent carbon dioxide and −144.8°C. No compounds were reported. (See figure 20.)

19. Carbon monoxide–nitrogen (29, 36, 38, 45)

Carbon monoxide, f.p. −204.9°C.; nitrogen, f.p. −210.0°C. No eutectic nor compound was found. A complete set of solid solutions was formed (29, 36, 38). (See the solid-line curve in figure 21.)

Carbon monoxide, f.p. −205.03°C.; nitrogen, f.p. −209.95°C. No eutectic nor compound was reported (45). (See the broken-line curve in figure 21.)

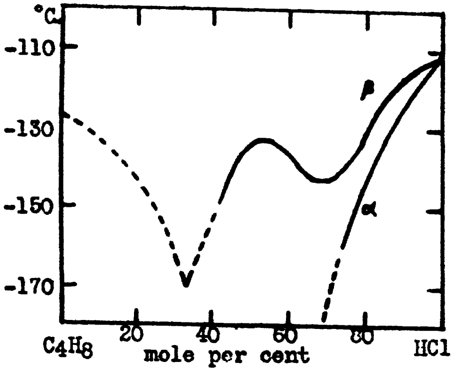

Fig. 19. Butylene–hydrogen chloride system

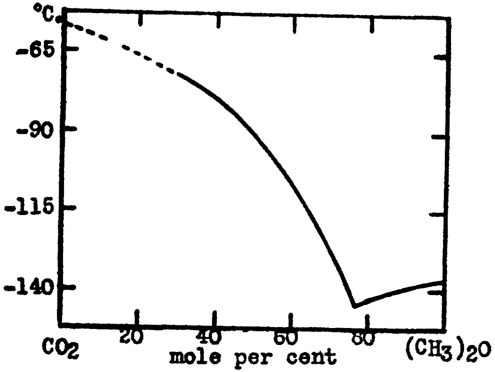

Fig. 20. Carbon dioxide–methyl ether system

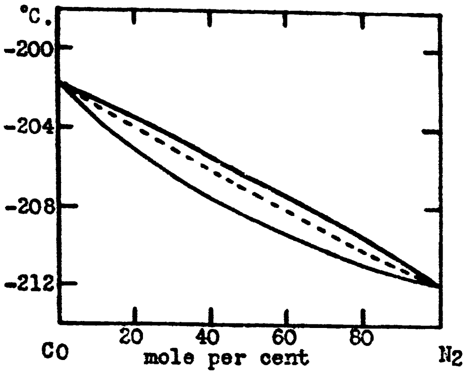

Fig. 21. Carbon monoxide–nitrogen system

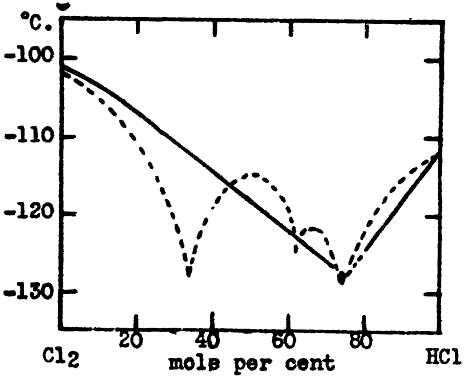

Fig. 22. Chlorine–hydrogen chloride system

20. Chlorine–hydrogen chloride (31, 47)

Chlorine, f.p. −101.5°C.; hydrogen chloride, f.p. −112.0°C. A eutectic occurred at 14.5 mole per cent chlorine and −127.5°C. No compound was reported. (See the solid-line curve in figure 22 (31).)

Chlorine, f.p. −102°C.; hydrogen chloride, f.p. −112°C. Eutectics were found at 26.3 mole per cent chlorine and −129°C., at 38.0 mole per cent chlorine and −125°C., and at 66.0 mole per cent chlorine and −128°C. The compounds $Cl_2 \cdot 2HCl$, f.p. −121°C., and $Cl_2 \cdot HCl$, f.p. −115°C., were reported. (See the broken-line curve in figure 22 (47).)

21. Chlorine–methyl chloride (46)

Chlorine, f.p. −102°C.; methyl chloride, f.p. −90°C. Eutectics occurred at 27.8 mole per cent chlorine and −124°C., at 44.1 mole per cent chlorine and −120°C., and at 63.3 mole per cent chlorine and −129°C. The compounds $Cl_2 \cdot 2CH_3Cl$, f.p. −120°C., and $Cl_2 \cdot CH_3Cl$, f.p. −122°C., were found. (See figure 23.)

22. Chlorine–nitrosyl chloride (19)

Chlorine, f.p. −94.4°C.; nitrosyl chloride, f.p. −64.5°C. A eutectic occurred at 57.5 mole per cent chlorine and −107.4°C. No compounds were reported. The freezing point given for chlorine is high, and the system should be reinvestigated. (See figure 24.)

23. Chlorine–sulfur dioxide (27, 41)

Chlorine, f.p. −100.9°C.; sulfur dioxide, f.p. −75.2°C. In the dark a eutectic was found at 97 mole per cent chlorine and −102.2°C. No compound was reported. In the light, eutectics were reported at 89 mole per cent chlorine and approximately −109.5°C. and at approximately 12 mole per cent chlorine and −84.5°C. (See figure 25.)

24. Ethane–hydrogen chloride (6, 7)

Ethane, f.p. −172.5°C.; hydrogen chloride, f.p. −111.6°C. Point of inflection is horizontally tangent at −125.2°C. No compound was reported. (See figure 26.)

25. Ethylene–hydrogen bromide (34)

Ethylene, f.p. approximately −167°C.; hydrogen bromide, f.p. −66.0°C. A eutectic occurred at approximately 85.4 mole per cent ethylene and −173.5°C., and there was a slight depression at approximately 51 mole per cent ethylene and −161°C. No compound was found. (See figure 27.)

26. Ethylene–methane (36, 37)

Ethylene, f.p. −169.1°C.; methane, f.p. −182.6°C. A eutectic occurred at 12.2 mole per cent ethylene and −188.6°C. No compound was reported. (See figure 28.)

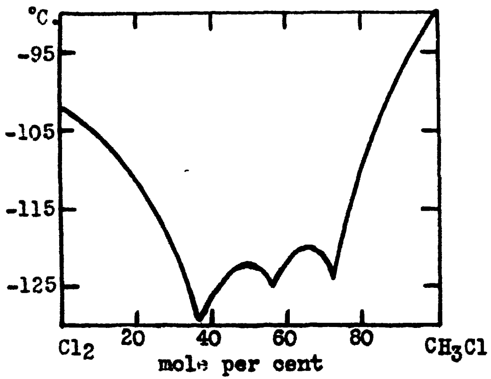

Fig. 23. Chlorine-methyl chloride system

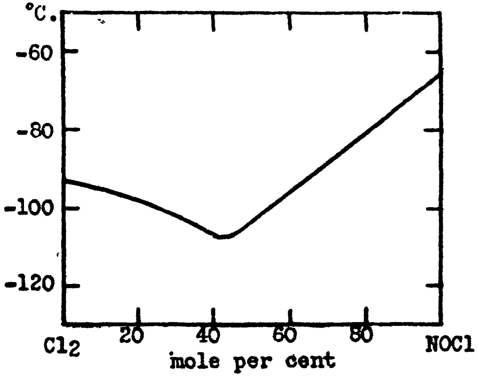

Fig. 24. Chlorine-nitrosyl chloride system

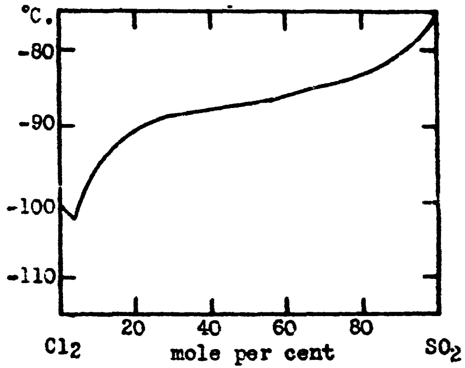

Fig. 25. Chlorine-sulfur dioxide system

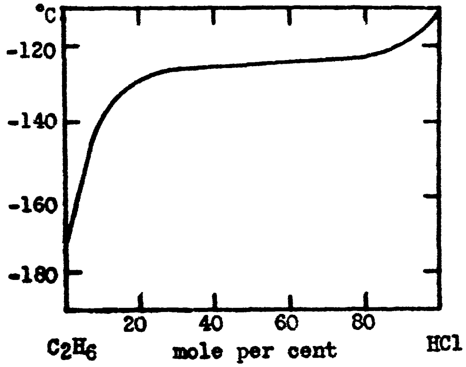

Fig. 26. Ethane-hydrogen chloride system

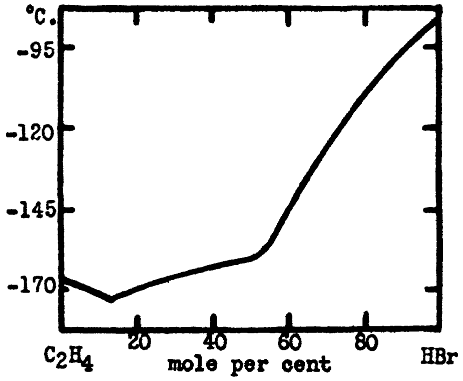

FIG. 27. Ethylene-hydrogen bromide system

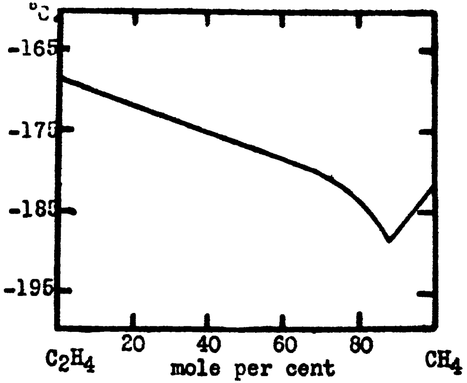

FIG. 28. Ethylene-methane system

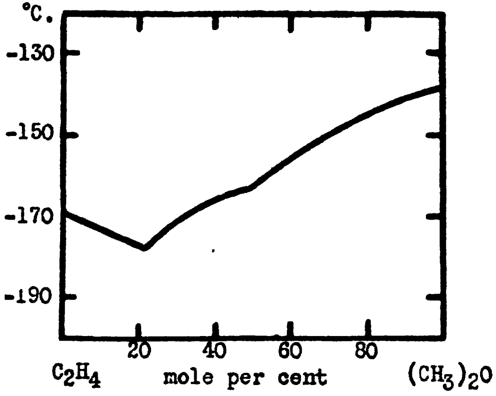

FIG. 29. Ethylene-methyl ether system

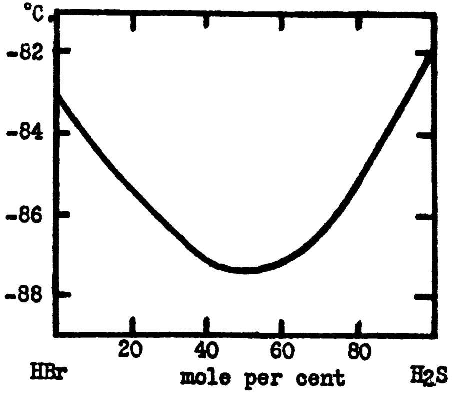

FIG. 30. Hydrogen bromide-hydrogen sulfide system

27. Ethylene-methyl ether (8)

Ethylene, f.p. −169.5°C.; methyl ether, f.p. −138°C. A eutectic occurred at 79.5 mole per cent ethylene and −178.5°C. The unstable compound $C_2H_4 \cdot (CH_3)_2O$, f.p. −163.2°C., was found. (See figure 29.)

28. Hydrogen bromide-hydrogen sulfide (1)

Hydrogen bromide, f.p. −83.0°C.; hydrogen sulfide, f.p. −82.0°C. A eutectic occurred at 49 mole per cent hydrogen bromide and −87°C. No compound was reported. (See figure 30.)

29. Hydrogen bromide--methyl ether (31)

Hydrogen bromide, f.p. −86.0°C.; methyl ether, f.p. −138.0°C. A eutectic occurred at approximately 68 mole per cent hydrogen bromide and −100°C. The compound $HBr \cdot (CH_3)_2O$, f.p. −13.0°C., was found. The diagram is incomplete. (See figure 31.)

30. Hydrogen bromide-propylene (34)

Hydrogen bromide, f.p. −86.0°C.; propylene, f.p. approximately −185°C. Eutectics occurred at approximately 26.7 mole per cent hydrogen bromide and −196°C., and at approximately 61.3 mole per cent hydrogen bromide and −167.3°C. The compound $HBr \cdot C_3H_6$, f.p. approximately −166.6°C., was found. (See figure 32.)

31. Hydrogen chloride-hydrogen sulfide (6, 7)

Hydrogen chloride, f.p. −111.6°C.; hydrogen sulfide, f.p. −82.6°C. A eutectic occurred at approximately 72 mole per cent hydrogen chloride and −117.5°C. No compound was reported. (See figure 33.)

32. Hydrogen chloride-methyl chloride (5)

Hydrogen chloride, f.p. −111°C.; methyl chloride, f.p. −93.0°C. A eutectic occurred at 72.7 mole per cent hydrogen chloride and −161°C. No compound was found. (See figure 34.)

33. Hydrogen chloride-methyl ether (2, 3, 4, 31)

Hydrogen chloride, f.p. −111°C.; methyl ether, f.p. −138.5°C. The compounds $HCl \cdot (CH_3)_2O$, f.p. −94°C., and $4HCl \cdot (CH_3)_2O$, f.p. −102°C., were found (2).

Hydrogen chloride, f.p. −111.3°C.; methyl ether, f.p. −138°C. Eutectics occurred at 7.5 mole per cent hydrogen chloride and −147°C., at approximately 62 mole per cent hydrogen chloride and −125°C., and at 91 mole per cent hydrogen chloride and −122°C. The compounds $HCl \cdot (CH_3)_2O$, f.p. −97.1°C., and $4HCl \cdot (CH_3)_2O$, f.p. −103°C., (4) and −102.8°C. (3), were found. (See the solid-line curve in figure 35.)

Hydrogen chloride, f.p. −112.0°C.; methyl ether, f.p. −138°C. Eutectics occurred at 93.3 mole per cent hydrogen chloride and −129°C., and at 66.6 mole

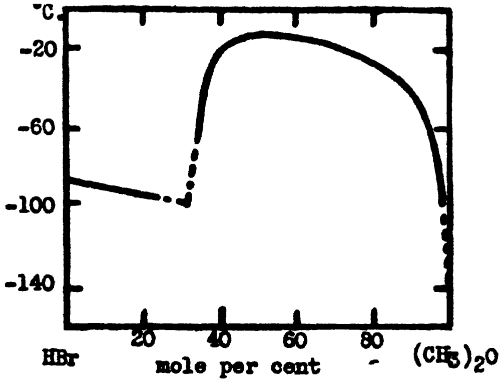

Fig. 31. Hydrogen bromide–methyl ether system

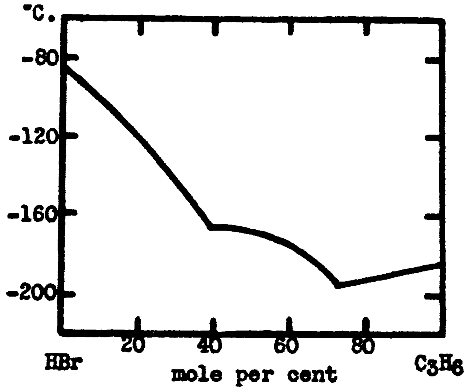

Fig. 32. Hydrogen bromide–propylene system

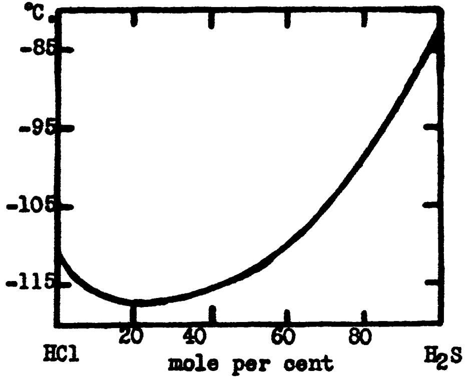

Fig. 33. Hydrogen chloride–hydrogen sulfide system

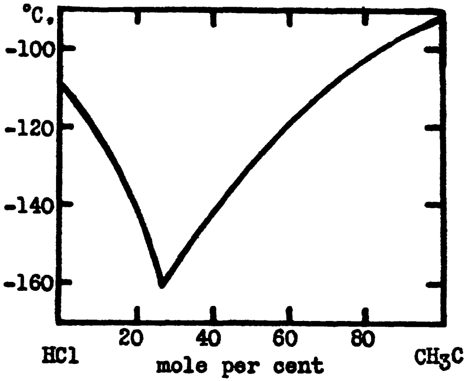

Fig. 34. Hydrogen chloride–methyl chloride system

per cent hydrogen chloride and −121.2°C. The compounds $HCl \cdot (CH_3)_2O$, f.p. −96°C., and 3 or 4 $HCl \cdot (CH_3)_2O$, f.p. −102°C., were found (31). (See the broken-line curve in figure 35.)

34. Hydrogen chloride–nitric oxide (35)

Hydrogen chloride, f.p. −113°C.; nitric oxide, f.p. −153°C. The freezing points were located by the aid of conductivity measurements. The freezing points of mixtures the mole fractions of which approached 0.5 could not be determined, because the gases condensed as pure solid phases. A homogeneous liquid phase was obtained, with a pressure of 15 to 20 atmospheres, which had no conductivity, indicating the complex $NOH^+ \cdot Cl^-$; this complex completely dissociated above −143°C. The freezing point given for nitric oxide is about 8°C. high.

35. Hydrogen chloride—sulfur dioxide (9, 10)

Hydrogen chloride, f.p. −112°C.; sulfur dioxide, f.p. −72°C. A eutectic occurred at 80 mole per cent hydrogen chloride and −133.5°C. No compound was reported. (See figure 36.)

36. Hydrogen iodide–hydrogen sulfide (1)

Hydrogen iodide, f.p. −46°C.; hydrogen sulfide, f.p. −82°C. A eutectic occurred at approximately 32 mole per cent hydrogen iodide and −90.8°C. No compound was found. (See figure 37.)

37. Hydrogen iodide–methyl ether (31)

Hydrogen iodide, f.p. −50.9°C.; methyl ether, f.p. not given. A eutectic occurred at 72.5 mole per cent hydrogen iodide and approximately −78°C. The compound $HI \cdot (CH_3)_2O$, f.p. −22°C., was found. The diagram is incomplete. (See figure 38.)

38. Hydrogen sulfide–methyl ether (12, 13)

Hydrogen sulfide, f.p. −83.3°C.; methyl ether, f.p. −137.6°C. Eutectics occurred at 64.5 mole per cent hydrogen sulfide and −153.7°C., and at 29.4 mole per cent hydrogen sulfide and −159.1°C. The compound $H_2S \cdot (CH_3)_2O$, f.p. −148.6°C., was found. (See figure 39.)

39. Hydrogen sulfide–sulfur dioxide (15)

Hydrogen sulfide, f.p. approximately −83°C.; sulfur dioxide, f.p. approximately −72.5°C. A eutectic was found at 76 mole per cent hydrogen sulfide and −110°C. No compound was reported. (See figure 40.)

40. Krypton–methane (42, 44)

Krypton, f.p. −157.1°C.; methane, f.p. −182.6°C. A complete set of solid solutions consisting of non-porous mixed crystals was obtained (44). (See the solid-line curve in figure 41.)

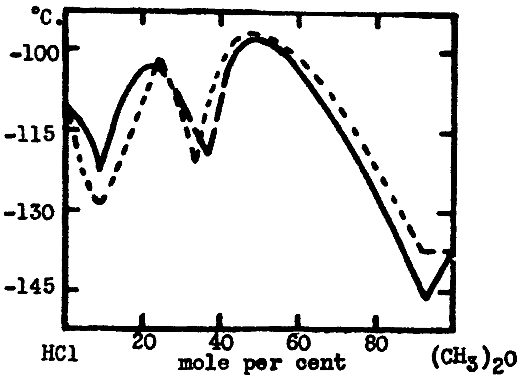

Fig. 35. Hydrogen chloride–methyl ether system

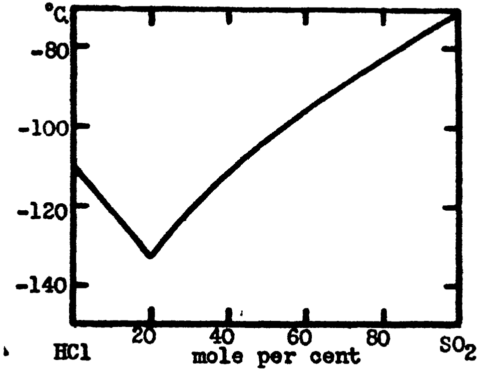

Fig. 36. Hydrogen chloride–sulfur dioxide system

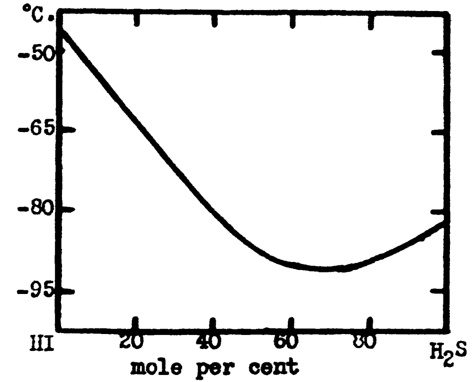

Fig. 37. Hydrogen iodide-hydrogen sulfide system

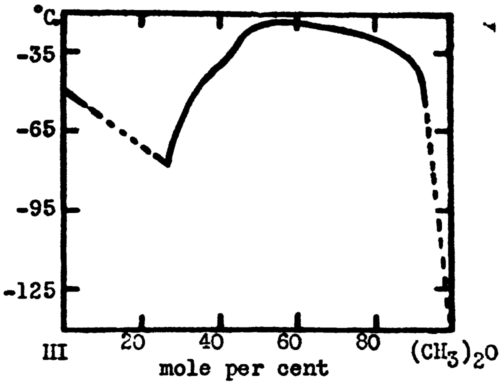

Fig. 38. Hydrogen iodide–methyl ether system

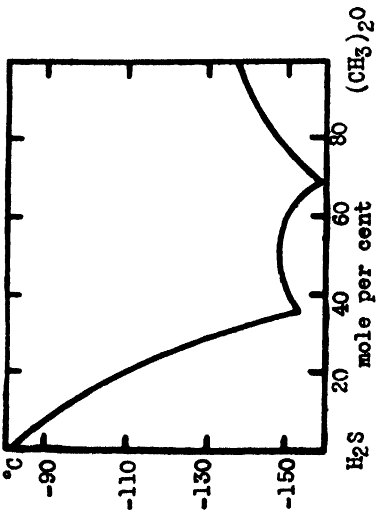

FIG. 39. Hydrogen sulfide-methyl ether system

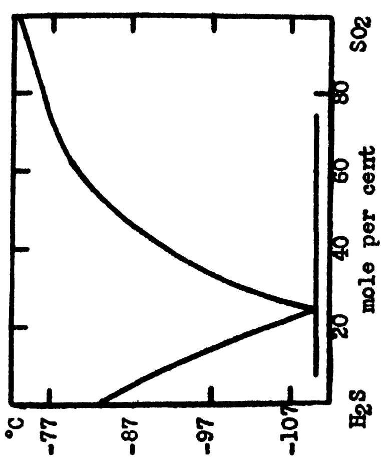

FIG. 40. Hydrogen sulfide-sulfur dioxide system

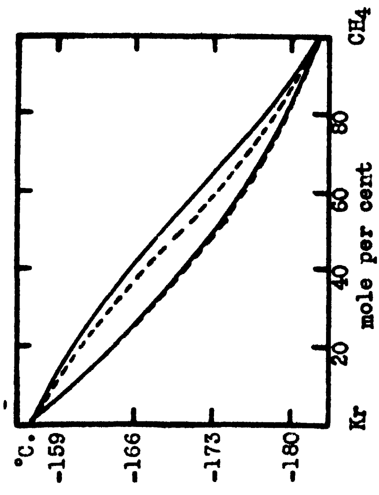

FIG. 41. Krypton-methane system

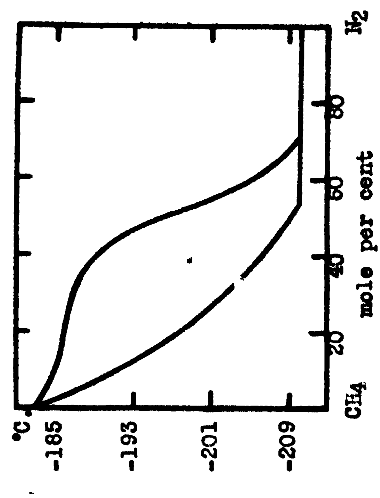

FIG. 42. Methane-nitrogen system

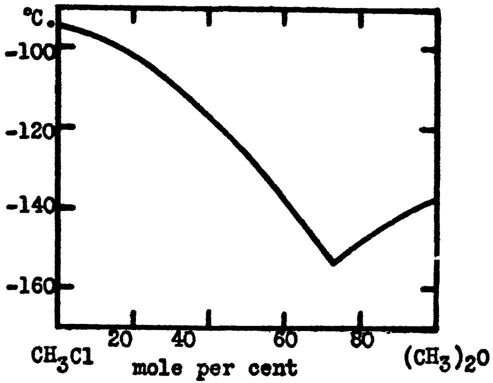

Fig. 43. Methyl chloride–methyl ether system

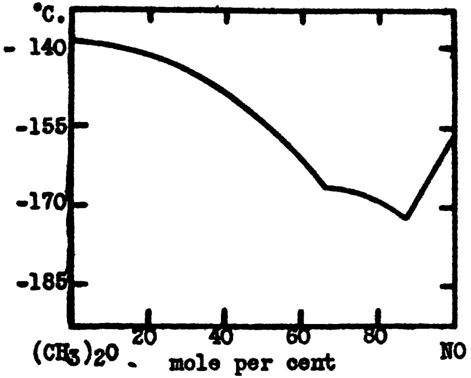

Fig. 44. Methyl ether–nitric oxide system

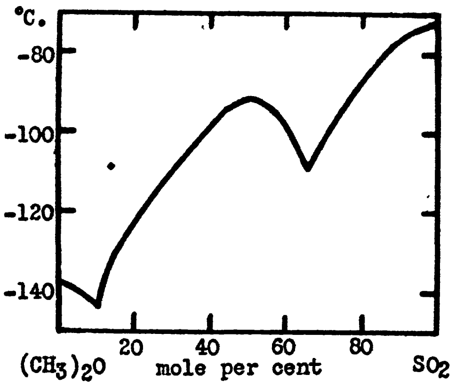

Fig. 45. Methyl ether–sulfur dioxide system

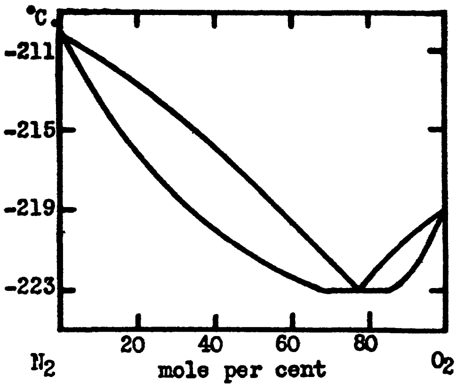

Fig. 46. Nitrogen–oxygen system

Krypton, f.p. −157.1°C.; methane, f.p. −182.6°C. A complete set of solid solutions was obtained. The data are not in too good agreement with the above work (42). (See the broken-line curve in figure 41.)

41. Methane–nitrogen (22)

Methane, f.p. −183.1°C.; nitrogen, f.p. −210.0°C. Peritectic point occurred around 30 mole per cent methane and −210.0°C. (See figure 42.)

42. Methyl chloride–methyl ether (2, 4)

Methyl chloride, f.p. −94.5°C.; methyl ether, f.p. −138.5°C. A eutectic occurred at 27 mole per cent methyl chloride and −154°C. No compound was reported. (See figure 43.)

43. Methyl ether–nitric oxide (8)

Methyl ether, f.p. −138°C.; nitric oxide, f.p. −161°C. A eutectic occurred at 12.5 mole per cent methyl ether and −172°C. The compound $(CH_3)_2O \cdot 2NO$, f.p. −166.3°C., was found. (See figure 44.)

44. Methyl ether–sulfur dioxide (2, 4)

Methyl ether, f.p. −138.0°C.; sulfur dioxide, f.p. −72.3°C. Eutectics occurred at 34 mole per cent methyl ether and −109°C., and at 88.5 mole per cent methyl ether and −144°C. The compound $(CH_3)_2O \cdot SO_2$, f.p. −91.5°C., was found. (See figure 45.)

45. Nitrogen–oxygen (29, 36, 38)

Nitrogen, f.p. −210.0°C.; oxygen, f.p. −219.0°C. A eutectic occurred at 22.5 mole per cent nitrogen and −223.0°C. No compound was reported. (See figure 46.)

VII. SUMMARY

A critical survey of the field of thermal analysis of liquefied gases has been made. The field was limited to binary systems in which both components were gases under standard conditions.

The methods used to establish mole fractions and to determine their freezing points were reviewed, and the procedure used at this laboratory was analyzed for possible sources of error.

Forty-five binary systems were found in the literature and the salient facts about each system presented. The phase-rule diagrams for forty-four of these systems were included. Errors in some of the work are obvious and some of these systems should be reinvestigated. These errors were probably due to impurities in the components, or to inferior methods for temperature measurements.

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ALICYCLIC-AROMATIC ISOMERIZATION

E. C. HORNING

Department of Chemistry, University of Michigan, Ann Arbor, Michigan

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CONTENTS

I. Introduction . . . 89
II. Isomerization with carbon–carbon bond fission . . . 92
  A. Different ring systems . . . 92
  B. Bridged six-membered rings . . . 100
  C. Rings with quaternary ring atoms . . . 102
III. Isomerization by redistribution of hydrogen . . . 104
  A. Nature of the isomerism . . . 104
  B. Methods of aromatization . . . 109
    1. Thermal . . . 109
    2. Acids (and bases) . . . 109
    3. Catalytic . . . 112
  C. Isomerizations involving carbon–carbon bonds only . . . 116
  D. Isomerizations involving carbon–oxygen bonds . . . 118
  E. Isomerizations involving carbon–nitrogen bonds . . . 129
IV. Summary . . . 131

I. INTRODUCTION

The distinction between aromatic and alicyclic compounds is based upon a number of properties which are common to aromatic structures and whose possession gives the molecule its "aromatic character." These properties may be used to define "aromaticity," or they may be regarded as manifestations of the nature of a structure which involves a ring system of the benzene type containing alternating double and single bonds.[1] Of these properties one of the most fundamental is the unusual stability of the ring system as compared with the stability to be expected in the light of alicyclic considerations. Thus, benzene is far more stable than the hypothetical alicyclic cyclohexatriene with non-interacting double bonds. This unusual stability is reflected quantitatively in the thermal data for the combustion and hydrogenation of benzene and for the dehydrogenation of dihydrobenzene (when compared with the calculated "alicyclic" values); it is also responsible for the non-existence of certain alicyclic isomers of aromatic compounds. For example, the keto forms (Ia, Ib) of phenol are thermodynamically unstable with respect to the enol form (phenol), and they are apparently incapable of existence as chemical individuals. This is also true of the alicyclic isomers of toluene (IIa, IIb). Such isomers have been postulated from time to time as reaction intermediates, and methylene lines have been reported from data gathered in absorption-spectra studies of toluene (90). However, the independent existence of these isomers as chemical individuals has never been observed, because of the great difference in stability between the alicyclic and aromatic forms, and because of the fact that the transition to the aromatic form occurs with such readiness that there is no practical way of preventing it.

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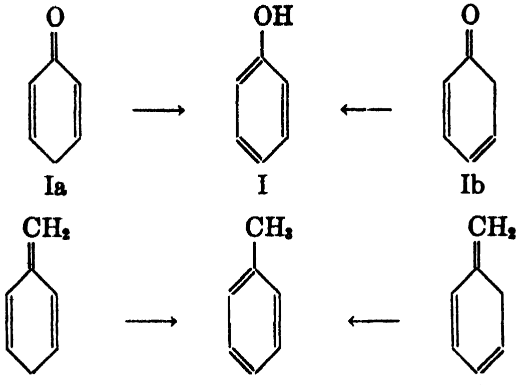
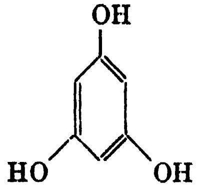
[1] For a critical discussion of "aromatic character" see L. F. Fieser in *Organic Chemistry*, edited by H. Gilman, 2nd edition, Vol. I, pp. 117-213 John Wiley and Sons, Inc., New York (1943).



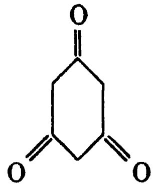
Ia I Ib

IIa II IIb

The isomerization of an alicyclic compound to an aromatic isomer is governed by two factors, and these illustrations present merely one specific form of the relation. The factors are (*1*) the relative thermodynamic stability of the two forms, and (*2*) the ease of transition from one form to the other. So far as the first factor is concerned, it is not to be assumed that the aromatic form is invariably the more stable; this will be generally true, but exceptions exist. For example, in the phloroglucinol–cyclohexanetrione equilibrium (III $\rightleftarrows$ IV), the fact that both phenolic and ketonic reagents acting on phloroglucinol yield characteristic derivatives indicates that these two structures have comparable stabilities. Little is known about the effect of polyfunctionality on the stabilization of alicyclic forms, but it seems evident that comparable stabilities of the two forms (alicyclic *vs.* aromatic) may exist for polyfunctional molecules but that the number of isomers with such a relation is probably small. In the case of polynuclear compounds this condition may be altered; this point will be discussed later.

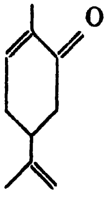


III
Phloroglucinol

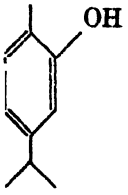


IV
Cyclohexanetrione

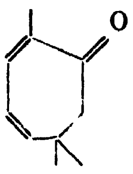
The ease of transition to the aromatic form is important in that it usually determines the possibility of separate existence for the alicyclic molecule. This is always true if the aromatic molecule has a far greater thermodynamic stability than its alicyclic isomers, a condition which is probably realized in almost every case. For example, carvone (V) is stable under ordinary conditions; it may be distilled under atmospheric pressure, and it may be carried through a number of reactions to yield the expected derivatives. However, the isomeric carvacrol (VI) is thermodynamically far more stable, and a variety of conditions will result in the isomerization of carvone to carvacrol. The aromatization is usually nearly complete and is generally rapid, sometimes violently so. Also, eucarvone (VII), which contains a seven-membered ring, exists as a chemical individual but the transition to the isomeric carvacrol (VI) occurs on heating.



V
Carvone



VI
Carvacrol



VII
Eucarvone

In general, the ease with which the isomerization occurs usually determines not only the possibility of separate existence but also the possibility of preparation of a given alicyclic isomer by a given method. There are many cases known in which aromatic compounds are isolated as the result of reactions which should lead instead to one of their alicyclic isomers. It is evident that in such cases the reagents or reaction conditions are those which also induce isomerization. There are, however, many alicyclic compounds isomeric with aromatic structures which have a separate existence of their own, and in these cases isomeric aromatization awaits only the establishment of appropriate conditions.

Studies of this type of isomerization contribute to a more extensive knowledge of the relation between alicyclic and aromatic systems. They are also of considerable interest from a practical point of view. If the isomerization requires the rearrangement of hydrogen atoms only, it can usually be carried out under relatively mild conditions, and no change other than that attendant upon the rearrangement of the unsaturation occurs. The relative positions of side chains and functional groups in the aromatic molecule are predetermined by their positions in the alicyclic isomer. A synthetic route to aromatic compounds involving the preparation of an alicyclic intermediate through typical aliphatic (or alicyclic) reactions, followed by isomeric aromatization, possesses, therefore, the singular advantage that the restrictions on its use are determined for the most part by the limitations of aliphatic reactions and not by those of aromatic reactions. Methods having this advantage provide a useful complement to the usual aromatic syntheses in which the ring structure is preserved.

The recognition of the usefulness of isomeric aromatization in synthesis is apparently not widespread, although there are many examples of such aromatizations in the literature. Some few have been described as synthetic methods, others are merely incidental observations, and some have apparently been taken as instances of anomalous behavior. The synthetic possibilities are far from exhausted, and a correlation of previous work may reveal new applications.

The classification scheme which has been adopted in this review is based on structural considerations. Since isomers are compounds whose only necessary relation is that they have the same molecular formula, it is apparent that a given aromatic compound may have a number of alicyclic isomers which differ in ring size, in degree of ring unsaturation, and in variety of ring or chain branching. The information now available indicates that six-membered rings in alicyclic isomers are those which are preserved, and which appear as aromatic nuclei after isomerization. Alicyclic compounds containing rings other than those of six members, such as those of five or seven members, or those with multicyclic ring systems, some of which are not six-membered, may undergo isomeric aromatization, but such rearrangements necessitate a change in the carbon skeleton of the molecule. Also, compounds containing a quaternary carbon atom in a six-membered ring cannot isomerize with aromatization of such a ring unless carbon–carbon bonds are broken and re-formed. On the other hand, if the alicyclic isomer contains a six-membered ring, appropriately substituted, it is often possible for the isomerization to proceed through the rearrangement or redistribution of the hydrogen atoms alone. There is no change in the skeleton, but the unsaturation distributed through the alicyclic structure becomes that which is associated with the aromatic ring or rings after isomerization.

Isomerizations involving fission of a carbon–carbon bond as a necessary feature of the rearrangement are treated in section II. Further classification within this group is based on the type of ring system in the alicyclic isomers. Section III deals with isomerizations which require the redistribution of hydrogen atoms alone. It is convenient to group these according to the type of multivalent links present in the alicyclic compounds. Rearrangements involving only carbon–carbon bonds form one group, those involving carbon–oxygen bonds form a second, and the third consists of rearrangements involving carbon–nitrogen bonds. Further classification in section III is based on the type of aromatic nucleus which results on isomerization.

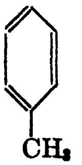
II. ISOMERIZATION WITH CARBON–CARBON BOND FISSION

A. DIFFERENT RING SYSTEMS

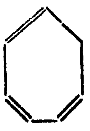
An aromatic compound and its alicyclic isomers may have totally different ring systems. For example, methylfulvene (I) and cycloheptatriene (tropilidene) (III) are isomers of toluene (II) and contain, respectively, rings of one less and

CHCH$_3$

I
Methylfulvene



II
Toluene



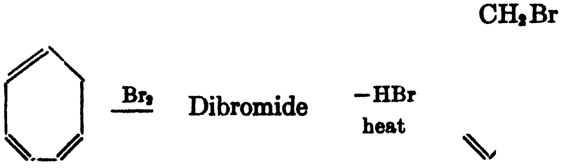
III
Cycloheptatriene

one more member than toluene. The isomeric aromatization of such molecules must involve, as a minimum change in the skeleton, the formation of a six-membered carbon ring through a new carbon–carbon bond, and the rupture of the original ring through fission of a carbon-carbon bond. An internal rearrangement of hydrogen atoms may or may not be required to complete the aromatization. While there is very little information available with regard to the relative thermodynamic stabilities of such molecules, it is probable that the aromatic compound is by far the most stable member of any such group. In the case of tropilidene, the heat of hydrogenation has been determined, and the difference between the value for tropilidene and that for cycloheptene, taken three times, is 6.7 kcal. per mole (25). This may be regarded as the resonance energy associated with the three double bonds of tropilidene. In the case of benzene the corresponding difference in energy is 36 kcal. per mole and, while these figures are not directly comparable, the order of difference is probably about the same as that for the difference in thermodynamic stability of tropilidene and toluene.

It is not to be assumed that a deviation from a ring of six members introduces a large amount of strain into the molecule and therefore confers immediately an increased thermodynamic instability on the alicyclic isomer. Alicyclic rings containing five atoms are very nearly strain free, since the bond angles in the ring are very close to those of the tetrahedral carbon atom. Six-membered rings are apparently very slightly strained, or may pass through positions of strain. Larger rings are very nearly free from strains of the Baeyer type, owing to their non-planar form, although the hydrogen blocking effect may induce a small added strain in rings of intermediate size (seven to eleven carbon atoms). These ideas are generally accepted for saturated rings, but the introduction of unsaturation should not increase the steric strain unless allene or acetylene unsaturation is introduced into a comparatively small ring. It is therefore probable that the differences in degree of stability between an aromatic compound and its alicyclic isomers of ring size of five or seven or more members are of very nearly the same order as the differences for compounds of the same ring size Rings of less than five members are omitted here because their appearance in alicyclic compounds which are isomeric with aromatic structures is limited at present to bridged-ring systems, which are taken up separately.

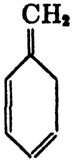
The size of the ring should therefore have comparatively little effect on the relative thermodynamic stability of an alicyclic compound with respect to an aromatic isomer, and the aromatic structure should be, in general, far more stable than any possible non-aromatic structure. So far as actual instability is concerned, most of the alicyclic isomers in this class are quite stable with regard to rearrangement. Tropilidene was isolated by both Merling and Ladenburg, and its structure was determined by Willstätter (140). It was synthesized by Willstätter from the 1,4-dibromide of cycloheptadiene by distillation from quinoline. During its purification it was in contact with dilute sulfuric acid, and it was distilled at atmospheric pressure (b p. 115.5–116.7°C.). The preparation was repeated a few years ago (1939) and the physical properties were determined more precisely (25, 73). There is no doubt as to its structure (catalytic hydrogenation yields cycloheptane), and the operations through which it has been carried indicate that it does not rearrange with great ease. It is true that the conditions to which tropilidene has been exposed were mild, but the preservation of the alicyclic form indicates at least moderate stability.

It is quite possible, however, to isomerize the tropilidene ring to an aromatic counterpart. The addition of one molecule of bromine, followed by heating on a water bath, results in the elimination of hydrobromic acid and formation of benzyl bromide (V) (88).



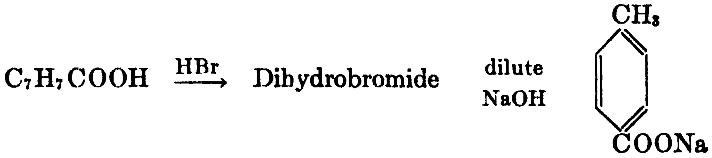
IV
Tropilidene

V
Benzyl bromide



IVa
(Merling)

This reaction was regarded at first as a confirmation of the dihydrobenzene structure (IVa) proposed by Merling for tropilidene, but it was recognized later that a ring contraction was involved. The same ring system is present in the tropilidenecarboxylic acid derived from anhydroecgonine (34, 35). From treat-



VI

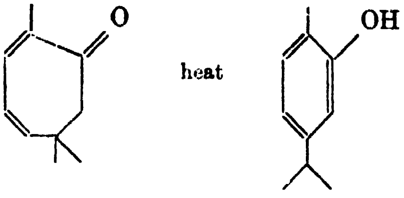
VII
Sodium *p*-toluate

ment of this acid with hydrobromic acid in acetic acid in a sealed tube at 100°C. there was obtained a dihydrobromide, and on boiling the latter with dilute sodium hydroxide there was obtained *p*-toluic acid (as the salt, VII). Willstätter[2] (141) established the structure of this tropilidenecarboxylic acid; the ring system is that of cycloheptatriene, and the rearrangement is due to an isomerization involving a contraction in ring size. It is unlikely that the addition of either bromine or hydrobromic acid to the tropilidene bond system would lead to a rearrangement, but it seems reasonable to believe that rearrangement accompanied dehydrohalogenation.[3]

---

[2] Willstätter's dissertation, "Über die Constitution und Reduction der *p*-Methylendihydrobenzoësäure," was completed in 1894. The methylenedihydrobenzene structure (for tropilidene derivatives) was accepted at the time, but no ring system of this type has ever been observed in an isolated individual, and further, it is probably an impossible structure as far as isolation under any type of condition now known is concerned. This was not realized at the time, but Willstätter later demonstrated the correct structure for many compounds related to tropilidene.

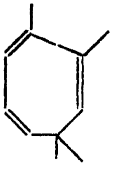
A seven-membered ring is also present in the cyclic unsaturated ketone eucarvone (VIII). Eucarvone is an isomer of carvacrol (IX), and its rearrangement to carvacrol may be effected by heating (11, 32). A closely related compound is the hydrocarbon X (or, less likely, XII), which has been prepared through the Grignard reaction from eucarvone and methylmagnesium iodide, followed by dehydration of the resulting tertiary alcohol (108). Isomeric aromatization of this compound to 2-methylcymene (XI) has not been observed.



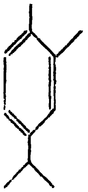
VIII
Eucarvone

IX
Carvacrol

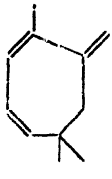
The literature with regard to alicyclic–aromatic isomerizations involving monocyclic rings of more than seven members appears to be limited to the conflicting evidence surrounding cycloöctatetraene. Willstatter's synthesis (142, 143) of this compound was carried out by way of cycloöctatriene (XIII). Cyclooctatriene is an isomer of the xylenes and ethylbenzene, but there is no doubt



X



XI
2-Methylcymene



XII

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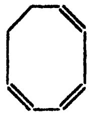
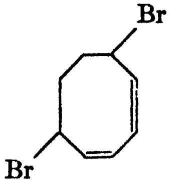
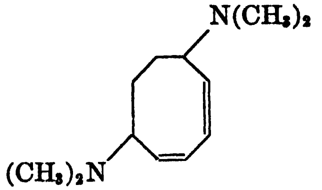
[3] It will be noted that the reactions which are included here, and which are termed isomerizations, may involve the formation of more or less definite intermediates. In some cases the reaction of isomeric aromatization proceeds as a rearrangement involving essentially only an initial and a final compound. In such cases a proposal of mechanism may require intermediates, but they are hypothetical in the sense that they are incapable of isolation and thus of direct experimental verification. In other cases an intermediate may have a more definite existence, in that it can actually be isolated. Reactions of the latter type are usually those in which addition of a reagent is followed later by expulsion of the elements which were added, the overall result being an isomerization. The present review includes reactions of both varieties.

as to its structure, and its isomerization to an aromatic compound was apparently not encountered. Addition of bromine led to XIV; this was converted to the di(dimethylamino)cycloheptadiene (XV), and the Hofmann procedure then yielded a hydrocarbon, presumably cycloöctatetraene (XVI).

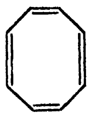

XIII
Cycloöctatriene

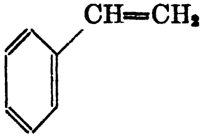


XIV



XV

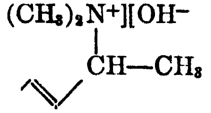

XVI
Cycloöctatetraene



XVII
Styrene

Within recent years (since 1939) there has been less certainty that the product in question was actually cycloöctatetraene. One objection (60) rests on the fact that more than one compound, isomeric in the positions of the double bonds, might have arisen from the several Hofmann reactions which were required. Another objection to the structure lies in the observation that the properties of the product resemble those of an aromatic isomer, styrene (XVII), very closely (52, 127).

In view of the rearrangements encountered for tropilidene, it does not seem improbable that styrene could have been one of the products. An intermediate

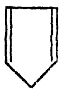


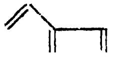
XVIII

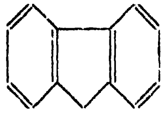
such as XVIII might have been formed through an isomerization involving ring contraction as the first step in the Hofmann procedure; this would lead to styrene on pyrolysis. A similar ring contraction might occur during the quinoline dehydrohalogenation of the dibromide XIV. This reaction, however, was not investigated beyond establishing the fact that the product was apparently not identical with the material obtained from the Hofmann reaction.

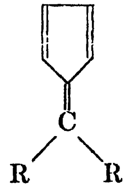
A reaction which may involve an isomerization is the conversion of cyclooctene to styrene over a chromium oxide catalyst at 425–455°C. in yields of 92–93 per cent (52). This conversion requires ring contraction and dehydrogenation with separate or simultaneous aromatization. To describe this as including an isomerization would indicate a more intimate knowledge of the mechanism than is available at present. It is not impossible, however, that the dehydrogenation proceeded to cycloöctatetraene and that this underwent isomerization on the catalyst surface. On the other hand, the ring may have undergone contraction prior to the dehydrogenation. The facility with which aromatic rings are formed at elevated temperatures on certain catalysts from such relatively remote precursors as larger saturated or unsaturated alicyclic rings and aliphatic saturated hydrocarbons indicates the special ability of such catalysts to promote the formation of aromatic rings. The exact nature of this process, as well as that of catalytic dehydrogenation in general, is not very clear, but in some cases such reactions may well involve dehydrogenation to an alicyclic compound isomeric with an aromatic structure, followed by isomerization to the latter.

The existence of rings of less than six members in alicyclic isomers of aromatic compounds is also quite possible. Here, however, the literature is apparently limited to the five-membered rings of the fulvene derivatives. Cyclopentadiene (XIX), indene (XX), and fluorene (XXI) all contain an active methylene group.

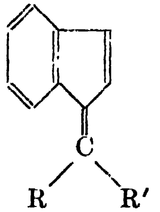

XIX
Cyclopentadiene


XX
Indene

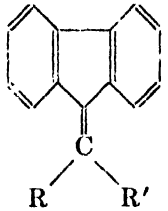

XXI
Fluorene



XXII



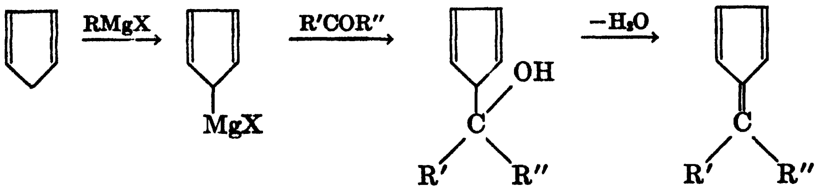
XXIII



XXIV

Condensation with aldehydes and ketones should result in the structures XXII to XXIV, which are derivatives of the parent hydrocarbon fulvene (XXII; R, R′ = H). The hydrocarbons from indene are benzofulvenes (XXIII), those from fluorene are dibenzofulvenes (XXIV), and in each case the compounds are isomeric with benzene, naphthalene, and phenanthrene (or anthracene) derivatives, respectively. Thiele (121, 122) obtained these compounds from condensations employing aliphatic ketones and aromatic aldehydes and ketones. Aliphatic aldehydes were unable to withstand the severity of his conditions. The reaction was reëxamined recently for several aliphatic aldehydes, in the case of fluorene, and a fulvene derived from butyraldehyde was isolated (115).

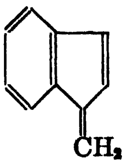
A second general investigation was described by Courtot (29), who employed a different preparative method. Cyclopentadiene and its analogs will form Grignard reagents by reaction with alkyl Grignard reagents. The reagents so prepared react with aldehydes or ketones to yield derivatives of the structure XXV, to which Courtot gave the name fulvanols. The alcohols underwent



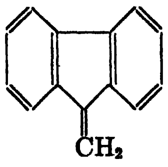
XXV XXII

dehydration easily to form the fulvenes, XXII. This method has the advantage that aliphatic aldehydes may be employed in the synthesis.

The fulvenes and benzofulvenes seem to be quite stable with respect to rearrangement, although in general they are quite reactive. No investigation of the possibility of isomeric aromatization of these compounds has been found in the literature. Benzofulvene (XXVI) was obtained by Courtot (29) from the passage of the corresponding fulvanol over alumina at 250°C. The product had



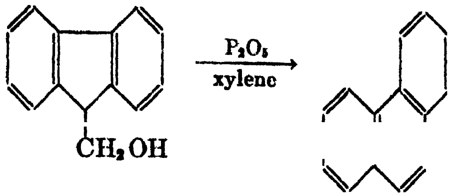
XXVI
Benzofulvene



XXVII
Dibenzofulvene

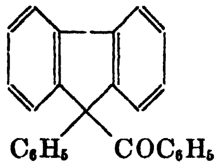
the odor of naphthalene, but did not have its physical properties (benzofulvene: m.p. 37°C., b.p. 95–97°C. at 17 mm.). It was highly reactive, but the rearrangement to naphthalene was not encountered. Dibenzofulvene (XXVII) was reported in 1904 (84) but the compound had none of the properties to be expected for such a structure. Its preparation, which was attempted several times without success (29, 30), was finally accomplished (119). It is a low-melting solid which polymerizes readily. No isomerization to phenanthrene was noticed.

While the isomerization of dibenzofulvene (XXVII) has not been observed directly, there is at least one instance in which the isomeric phenanthrene has been obtained by a reaction which should presumably lead to dibenzofulvene. When 9-fluorenylcarbinol (XXVIII) is dehydrated by refluxing over phosphorus pentoxide in xylene there is obtained, instead of the expected dibenzofulvene (XXVII), a nearly quantitative yield of phenanthrene (XXIX) (19). The reaction probably involves a Wagner rearrangement, perhaps similar to that observed in the hydriodic acid–red phosphorus reduction of phenylbenzoylfluorene (XXX). The first product here is presumably the alcohol XXXI, which then rearranges with dehydration to yield 9,10-diphenylphenanthrene (XXXII) (139). A number of Courtot's dehydrations of the fulvanols were carried out under acid conditions, but he apparently did not find any instances of similar rearrangements.

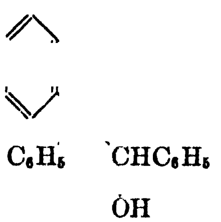


XXVIII
9-Fluorenylcarbinol

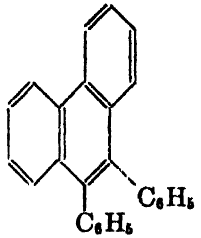
XXIX
Phenanthrene



XXX
Phenylbenzoylfluorene

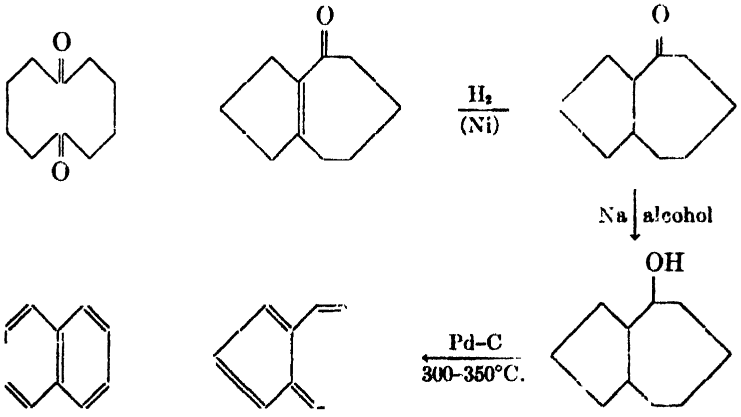


XXXI



XXXII
9,10-Diphenylphenanthrene

In the field of bicyclic compounds there are a number of examples of isomerization to aromatic structures. In most of these, a bridged ring structure contributes to the formal amount of unsaturation present, and isomeric aromatization requires rupture of one of the rings. Such reactions are considered in the next group, but there is one interesting example of alicyclic-aromatic isomerism which involves bicyclic structures for both compounds; this is the azulene–naphthalene isomerism. The azulenes are hydrocarbons, usually an intense blue or blue-

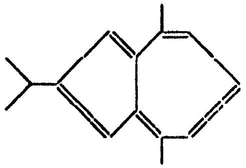


XXXIV
Napthalene

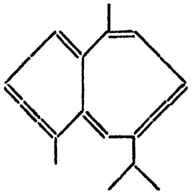
XXXIII
Azulene

violet in color, which may be obtained from a number of essential oils after subjection of the oils to dehydrogenation conditions, such as heating with sulfur, selenium, or palladium–charcoal (53). The elucidation of the structure of these compounds has been due largely to the efforts of Pfau and Plattner (98, 99, 100, 101). The parent hydrocarbon, azulene (XXXIII), may be prepared by the series of reactions shown; it is an isomer of naphthalene (XXXIV) but it has one seven- and one five-membered ring instead of two six-membered rings (99). A number of alkyl- and dialkyl-azulenes have also been prepared (98, 101), as has vetivazulene (XXXV) (100). Vetivazulene and *S*-guaiazulene (XXXVI) may both be obtained from certain essential oils; they are isomers of cadalene (XXXVII).

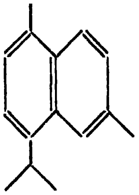
That this bond system, isomeric with that of the aromatic naphthalene nucleus, may be produced as the result of high-temperature dehydrogenations with sulfur or selenium, or catalysts such as palladium–charcoal or nickel, indicates certainly that the system has a high degree of stability. Calculations based on the heats of combustion of guaiazulene and cadalene, assuming that the side chains are equivalent, indicate that the azulene molecule has only about 8 per cent less bonding energy than naphthalene (96). Dehydrogenation catalysts are apparently unable to distinguish the combination of five- and seven-membered rings from the two six-membered rings of naphthalene, or, it may be that isomerization to a naphthalene system will occur over such catalysts, but that temperatures higher than those heretofore employed are required.



XXXV
Vetivazulene



XXXVI
S-Guaiazulene

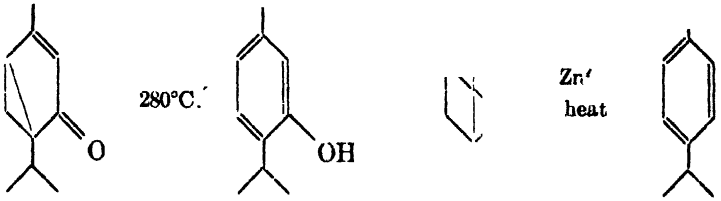


XXXVII
Cadalene

B. BRIDGED SIX-MEMBERED RINGS

There are a number of alicyclic compounds whose molecular formulas are the same as than of aromatic compounds, and whose structures include a six-membered ring. However, the formal unsaturation, or that which is indicated by the molecular formula, is not due entirely to multiple bonds, but is contributed to, in part, by a ring bridge. The isomerization of these compounds therefore includes of necessity a rupture of one of the rings, followed by redistribution of the hydrogen atoms. The examples to be found in the literature indicate that six-membered rings are preserved, and that the rings which are likely to be broken are those with three or four members.

An example of a reaction in this group is the transformation of umbellulone (I) into thymol (II) on heating at 280°C. (33). The cyclopropane ring is broken, and the molecule aromatizes, the alicyclic ketone thus being converted into a phenol. Another example is the conversion of verbenene (III) into the isomeric cymene (IV), by treatment with zinc chloride (17, 111).



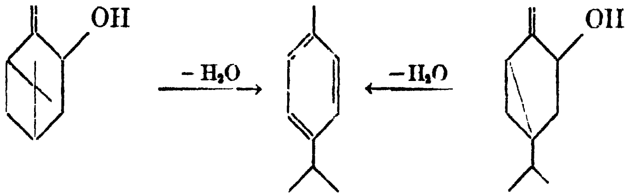
I Umbellulone

II Thymol

III Verbenene

IV Cymene

There are also several dehydration reactions which convert terpene alcohols into aromatic hydrocarbons, and which seem to involve rearrangements of this type. Both pinocarveol (V) (130), and sabinol (VI) (49) yield cymene (IV) under the influence of acid-type dehydrating agents. In both cases the reaction

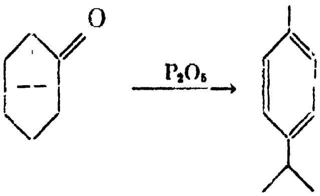


V Pinocarveol

IV Cymene

VI Sabinol

probably proceeds through the elimination of water to yield a bicyclic hydrocarbon, followed by rearrangement of the latter under the influence of the dehydrating agent. This is almost certainly true for pinocarveol (V), since the expected product of dehydration is verbenene (III), and it is known that acidic dehydrating agents will convert verbenene to cymene. A closely related reaction may be involved in the conversion of camphor (VII) into cymene (IV)

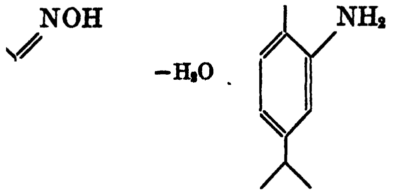


VII Camphor

IV Cymene

by the action of phosphorus pentoxide (5). In this case dehydration and isomerization are probably inseparable.

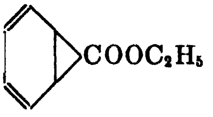
Another reaction which may belong in this group is the formation of carvacrylamine (X) from β-thujone oxime (IX) by the action of alcoholic sulfuric acid or zinc chloride (124). This reaction is closely related to those discovered by Wolff (section III, page 130) in which oximes of certain unsaturated cyclic ketones are dehydrated with isomerization to yield aromatic amines.



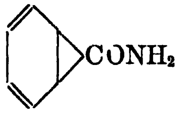
IX
β-Thujone oxime

X
Carvacrylamine

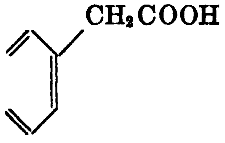
The action of diazoacetic ester on aromatic hydrocarbons leads to bicyclic esters. The compound from benzene is the ester of $\Delta^{2,4}$-norcaradiene-7-carboxylic acid (or $\Delta^{4,6}$-bicyclo[0.1.4]heptadiene-7-carboxylic acid). These compounds, also known as pseudo-arylacetic esters, were investigated extensively



XI



XII

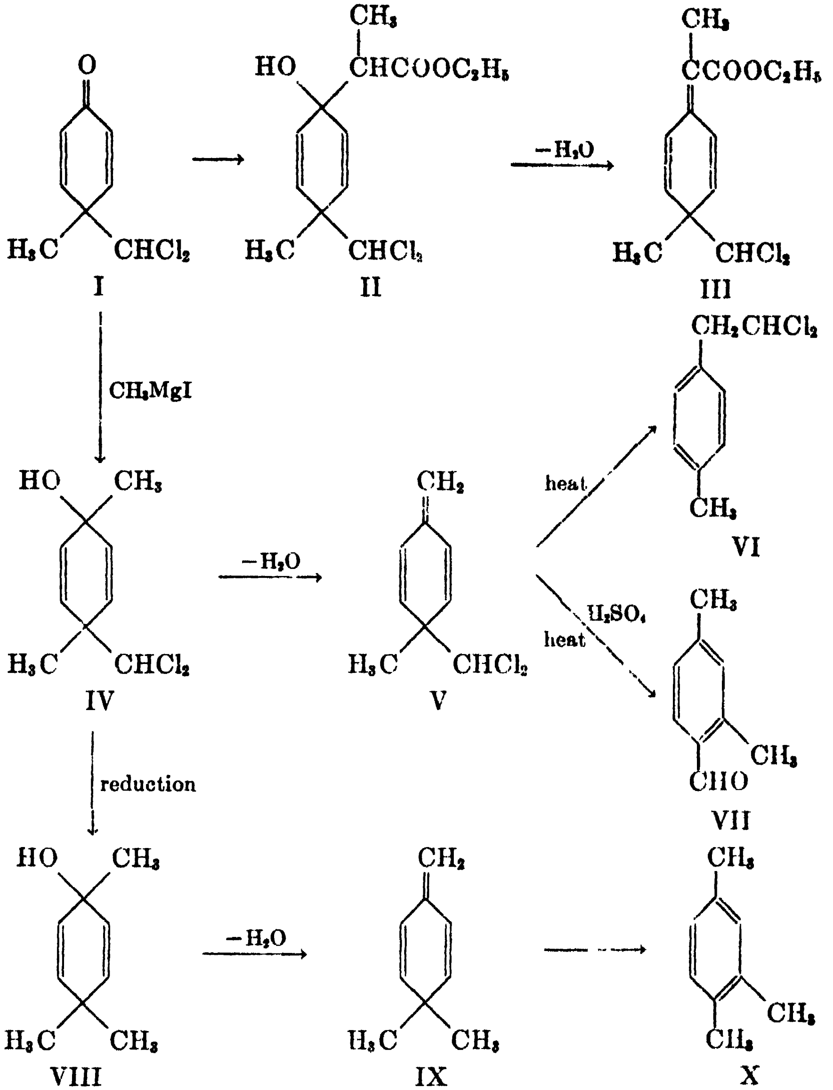


XIII

by Buchner (20). Most of the amides, such as XII (and also other acid derivatives), yield the corresponding isomeric arylacetic acid derivatives (or acids, XIII) on hydrolytic treatment with sulfuric acid. The cyclopropane ring is broken and isomerization follows.

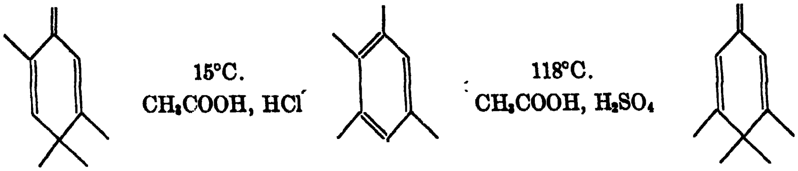
C. RINGS WITH QUATERNARY RING ATOMS

The principal members of this group are the semibenzenes of von Auwers (7). The term semibenzene is usually employed to designate alkylidenedimethyldihydrobenzenes having a structure similar to IX, but a number of related compounds with the same ring system were prepared by von Auwers. Some of the compounds involved in a typical series of reactions are illustrated. If *p*-cresol is treated with chloroform in an aqueous alkaline solution one of the products is the substituted cyclic dienone I. This ketone may be carried through both Reformatsky and Grignard reactions. The product of the Reformatsky reaction with ethyl α-bromopropionate is the tertiary alcohol II, which may be dehydrated to yield the ester III. Free acids having this structure rearrange readily to acids containing the benzene ring. The product of the Grignard reaction with methylmagnesium iodide and the ketone I is the tertiary alcohol IV. The halogen atoms may be removed by reduction to yield the alcohol VIII. Alcohols IV and VIII lose water easily to yield the semibenzene type of structure (V, IX). The chloro compound V rearranges on heating with migration of the dichloromethyl group to yield the aromatic isomer VI, while sulfuric acid causes the methyl group to migrate and hydrolyzes the dichloromethyl group, the result being *m*-xylylaldehyde (VII). The semibenzene IX isomerizes readily under the influence of acids to the aromatic isomer 1,2,4-trimethylbenzene (X).



The semibenzene ring system is stabilized by the presence of two substituent groups on one of the ring carbons. This quaternary carbon removes the possibility of aromatization by rearrangement of hydrogen atoms alone, but in general such compounds, while sufficiently stable to allow isolation, isomerize readily to the corresponding aromatic isomers. In the case of the semibenzenes one of the *gem*-methyl groups migrates during isomerization to the adjacent position, if this is open, and such rearrangements take place very easily. The semibenzene

XI isomerizes to pentamethylbenzene (XII) at 15°C. under the influence of hydrochloric acid in acetic acid. If both adjacent positions are blocked, the semibenzene will still isomerize but more vigorous conditions are required. For



XI XII XIII

example, compound XIII requires a much higher temperature (118°C.) for rearrangement to the same aromatic isomer, pentamethylbenzene (XII).

It is also possible to obtain trichloro compounds similar to I by the reaction of *p*-cresol with carbon tetrachloride and aluminum chloride. Phenols substituted in the ortho position, such as *o*-cresol, will also yield ketodihydrobenzenes, but the Grignard reactions of these ketones follow a different course involving 1,4-addition. The resulting products are not semibenzenes.

III. ISOMERIZATION BY REDISTRIBUTION OF HYDROGEN

A. NATURE OF THE ISOMERISM

All aromatic compounds contain a certain minimum amount of unsaturation which is associated with the ring system and which finds expression in both the molecular formula and in the usual aromatic ring structures involving double and single bonds. For example, the Kekulé formula for benzene and its derivatives indicates that such compounds contain, as a minimum, an amount of unsaturation formally equivalent to three carbon–carbon double bonds, and that this unsaturation is associated with the ring. A number of alicyclic isomers of aromatic compounds have been described in section II, but they have all required for isomerization the rupture and re-formation of at least one carbon–carbon bond. It is quite possible, however, for an aromatic compound and an alicyclic isomer to differ in the distribution of the multivalent links only, or, more precisely, in the arrangement of the hydrogen atoms alone. Isomerization in these cases requires only the redistribution of the hydrogen atoms so that the ring or rings acquire, through this process, an amount of unsaturation corresponding to the Kekulé type of structure.

This type of isomerization, which might be called isoaromatization, is best defined by reference to a few simple illustrations (table 1).

It will be observed that the unsaturation which is present in the aromatic ring as a carbon–carbon double bond need not appear in this form in the alicyclic isomer. In simple cases it may appear as carbon–carbon triple bonds, or multivalent carbon–oxygen or carbon–nitrogen bonds. Presumably it could also appear in the form of other multivalent links, as those of sulfur–oxygen or nitrogen–oxygen, but no examples of isomerization involving such bonds have been found in the literature. It will also be observed that even very simple

TABLE 1

Examples of isoaromatization

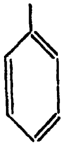
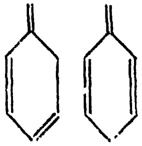
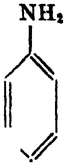
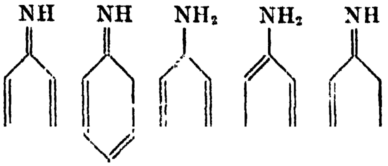
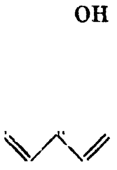
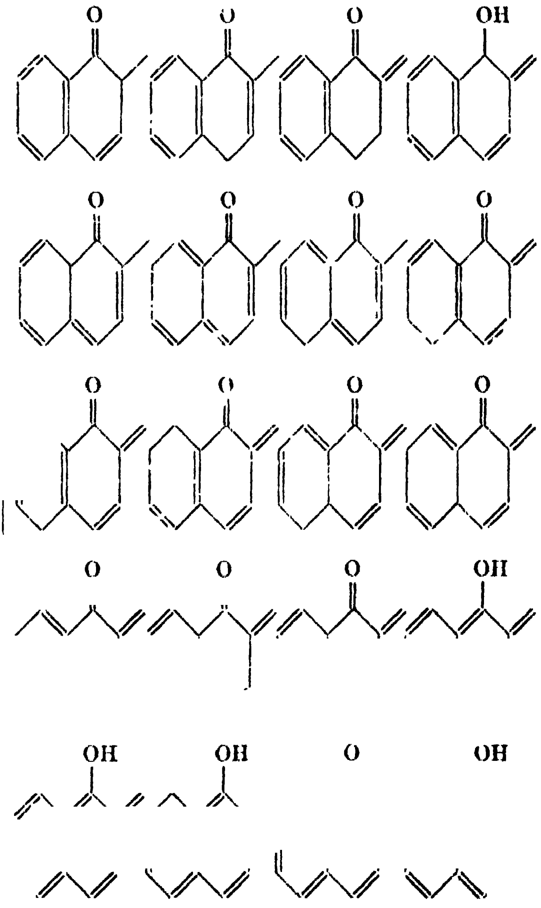
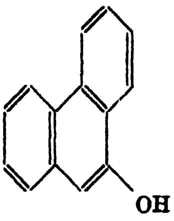
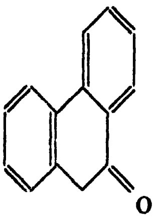
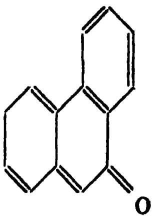
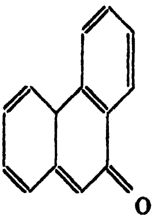
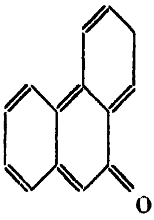
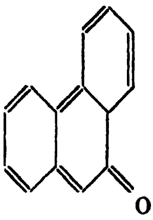
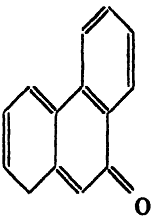
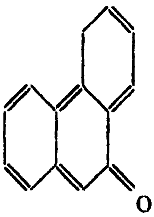
AROMATIC COMPOUND	ALICYCLIC (NON-AROMATIC) ISOMERIC STRUCTURES
Toluene, 	
p-Toluidine, 	
2-Methyl-1-naphthol, 	

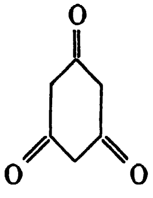
TABLE 1—*Concluded*

AROMATIC COMPOUND	ALICYCLIC (NON-AROMATIC) ISOMERIC STRUCTURES
9-Phenanthrol, 	      

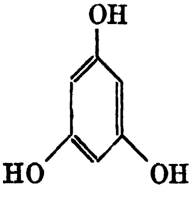
aromatic compounds may have a large number of alicyclic isomers of this type. (There is no attempt here to classify isomers as "possible" or "impossible," except that allene and acetylene bonds have been excluded from the rings. Nonaromatic keto–enol pairs are taken as two isomers.)

This variety of isomerism can also be extened to polynuclear compounds. In this case the alicyclic isomers are taken to include all isomers which are not entirely aromatic in nature. Thus, α-naphthols have among their isomers the corresponding α-tetralone derivatives. The "alicyclic isomer" here contains one aromatic ring, but the process of isomerization is essentially that of the isomeric aromatization of an alicyclic ring, and consequently these molecules are classified as alicyclic isomers. Examples of naphthalene and phenanthrene isomerism are shown in table 1.

The isomerization of any one of these alicyclic compounds to its aromatic isomer is governed by the two factors noted in the introduction: (*1*) the relative thermodynamic stability of the two forms, and (*2*) the ease of transition from one form to the other. Comparatively little quantitative data is available with respect to the first factor, but it is probable that for any monofunctional benzene or naphthalene derivative the aromatic form will be thermodynamically far more stable than any possible alicyclic isomer.[4] The chief item responsible for this difference in stability derives from the resonance energy of the aromatic system. This energy differential, which arises through aromatization of the ring or rings, is large enough to overshadow any energy effects due to the transformation of a single functional group in an alicyclic isomer. In the case of polyfunctional compounds this may or may not be true. The cyclohexanetrione–phloroglucinol equilibrium (I $\rightleftharpoons$ II) previously noted is one well-established instance in which the members of a pair of alicyclic–aromatic isomers have comparable stabilities.

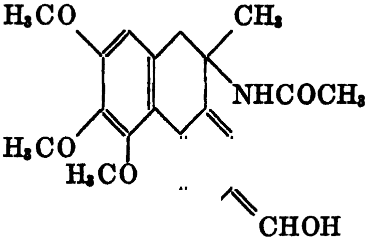


I

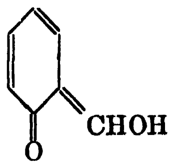


II

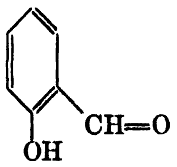
Colchiceine (III) (54) has in part a bond system corresponding to the hydroxymethylene form (IV) of salicylaldehyde (V), but the very fact that it does not isomerize during preparation casts some doubt on the proposed structure. There may be other cases in which two forms (alicyclic *vs.* aromatic) exist at very nearly the same energy levels, but there can be no doubt that these situations rarely occur.



III
Colchiceine



IV

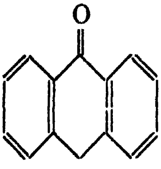


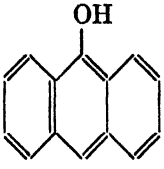
V
Salicylaldehyde

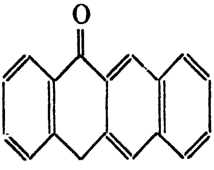
For polynuclear aromatic molecules the energy relations with respect to alicyclic isomers may be quite different. As a matter of fact, in some keto–phenol pairs the alicyclic form may have a much greater thermodynamic stability than the aromatic phenolic isomer. For example, the ketones anthrone (VI) and 2,3-benz-9-anthrone (VIII) may be isomerized to the corresponding phenols VII and IX, but the equilibrium in the latter case is greatly in favor of the keto form. The anthrone ⇌ anthranol equilibrium (VI ⇌ VII) in some solvents lies on the side of the keto form (in alcohol the equilibrium mixture contains about 90 per cent anthrone), but the ketone is soluble in alkali, indicating complete

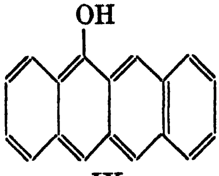
---

[4] Quantitative estimates of the energy differences for several aromatic-non-aromatic isomeric systems have been made from time to time. Phenol, for example, is estimated to be thermodynamically more stable by 16 kcal. per mole than its keto form. A brief discussion of several current estimates of this type may be found in *The Theory of Organic Chemistry* by Branch and Calvin (18).


VI
Anthrone


VII


VIII
2,3-Benz-9-anthrone


IX

isomerization under these conditions. The ketone VIII, however, will not dissolve in alkali and forms the anthranol-type acetate very much less readily than anthranol itself (42). Any generalization about energy relationships for polynuclear molecules must therefore be made with considerable caution, and for the most part the best procedure is to treat each such case individually.[5]

In all cases of this type of isomerism in which the energy relations favor the aromatic compound, and therefore in the great majority of all such cases, it is apparent that the second factor is the one which will usually determine the possibility of preparation, isolation, and continued existence of a given alicyclic isomer. In the event that the aromatization requires a rearrangement of hydrogen atoms that can be accomplished by a single tautomeric shift such as that of the keto-enol variety, the alicyclic isomers of the benzene and naphthalene series have no existence as chemical individuals, so far as is now known. Any preparative method designed to yield such a compound results in the aromatic isomer instead, simply because of the ease with which the tautomeric shift is brought about.

In the event that the alicyclic isomer has more than one exocyclic set of un-

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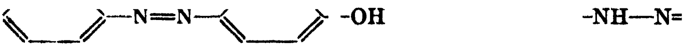
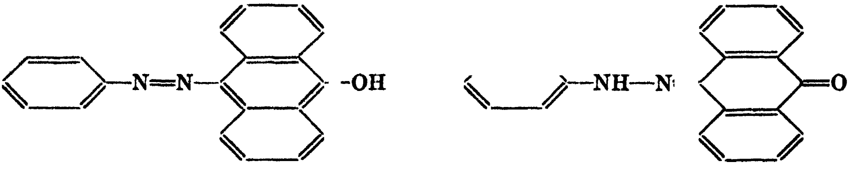
[5] Another example of the effect of polynuclear systems on aromatic-non-aromatic equilibria is shown by a comparison of the equilibria



(A)

Benzeneazophenol



(B)

Benzeneazoanthranol

encountered in the case of benzeneazophenol (A) and benzeneazoanthranol (B). The former apparently exists only as the azo compound, while the latter seems to be exclusively in the hydrazone form. The corresponding azonaphthol is an intermediate case so far as energy effects are concerned, and both structures are present in the equilibrium mixture (18).

saturated bonds, or if only one unsaturated bond set exists which is not in the ring but is distant at least one carbon from the ring, there is a possibility of independent existence as a chemical individual. In some of these instances isomeric aromatization can be brought about very readily, as for example by contact with acids. Also, since the isomerization involves essentially an intramolecular disproportionation of hydrogen, it is to be expected that catalysts which are useful for the intermolecular transfer of hydrogen should also be of value in this connection. Actually, it has been found that a number of isomeric aromatizations proceed under surprisingly mild conditions in the presence of hydrogenation catalysts.

It should be noted that it is characteristic of this type of isomerism that the skeleton of the molecule is not affected by the isomerization. Functional groups undergo transformation, such as keto–phenol transformation, but all substituents on the original alicyclic ring retain their positional relation during isomerization. This property is of considerable value from the point of view of synthetic applications of isomeric aromatizations. Many various types of specific isomerizations which have been encountered in the literature are described subsequently and provide an adequate demonstration of this point.

B. METHODS OF AROMATIZATION

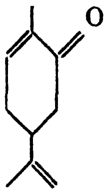
1. *Thermal*

Since a number of isomeric aromatizations are known which take place easily, there have been several attempts to induce a purely thermal conversion. The disturbance of bond systems under the impact of thermal energy is a common effect, but the disturbances often result in molecular degradation, and the method is therefore not attractive. There is a report that a thermal aromatization of carvone is possible (32), but as a result of other investigations it has also been reported that a catalytic agent of some sort is necessary (11, 105). At high temperatures (heating in an autoclave with clay chips at 450°C.) a partial conversion to carvacrol has been observed (126). Since acids and hydrogenation catalysts have proved to be simple and effective agents for inducing isomerization, further investigation of thermal effects has been discouraged.

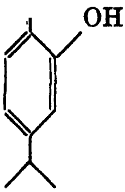
2. *Acids (and bases)*

The use of acids and bases to bring about rearrangements leading to aromatization involves a type of action which in the past was often referred to as catalytic, although this term is best reserved for the action of agents such as hydrogenation catalysts. Rearrangements induced by acids usually involve addition to unsaturated bonds; the addendum is subsequently lost, however, so that it does not appear in the final product. If the life span of the intermediate or intermediates is sufficiently long (under the reaction conditions), one or more of them can often be isolated from the reaction mixture. Such relatively long-lived intermediates have been isolated in a number of cases. Reactions involving the addition of hydrogen bromide or hydrogen chloride, followed by expulsion of the elements which were added, sometimes yield such compounds. On the other hand, if the intermediate is short-lived, it may enjoy no better than a hypothetical existence. Ionic intermediates resulting from addition of a proton are of this nature.

Acids, and in particular mineral acids, are usually very effective agents for



I
Carvone

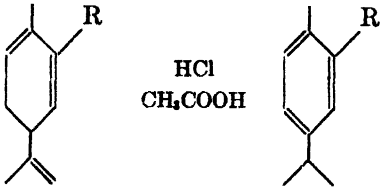


II
Carvacrol

inducing isomerization. For example, the rearrangement of carvone (I) to carvacrol (II) under the influence of acids was first observed about a century ago.

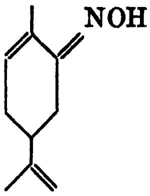
Acids and acid derivatives, as phosphoric, hydrochloric, and formic acids and phosphorus oxychloride, have been employed (61, 63, 74, 93, 104, 116, 128). The compound obtained from the combination of carvone and hydrogen chloride also yields carvacrol on heating with or without added acid catalysts (93). The yields are usually high and the conversion is fairly rapid, sometimes vigorous. Under circumstances not directed to the formation of carvacrol, but which involve contact of carvone with acid, it is to be expected that carvacrol will be among the products. Such is the case in the preparation of carvone hydrate by treatment of carvone with sulfuric acid (69, 110).

If carvone is allowed to react with a Grignard reagent (RMgX, R = methyl, ethyl, *n*-propyl, or phenyl) there results a tertiary alcohol or the product of its dehydration (64, 66, 72, 107, 109). The latter, which can be obtained from the alcohol and which has the structure III, can be aromatized readily to the corresponding hydrocarbon IV by heating in a dilute (2 to 3 per cent) solution of hydrogen chloride in acetic acid.

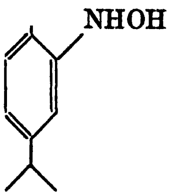


III IV

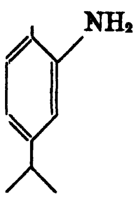
Another compound from carvone, the oxime (V), has the same ring structure as carvone, and has been found to yield carvacrylamine (VII) under the influence of potassium hydroxide (131) and of sulfuric acid in alcohol (132). Zinc and acetic acid and potassium hydroxide will also induce the conversion of isocarvone oxime to carvacrylamine (51, 137). The carvone oxime reactions probably involve rearrangement to the corresponding aromatic isomer VI (a hydroxylamine), followed by reduction to the amine VII. This seems more likely than a preliminary reduction to the imine (VIII), followed by rearrangement.



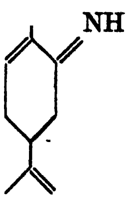
V



VI

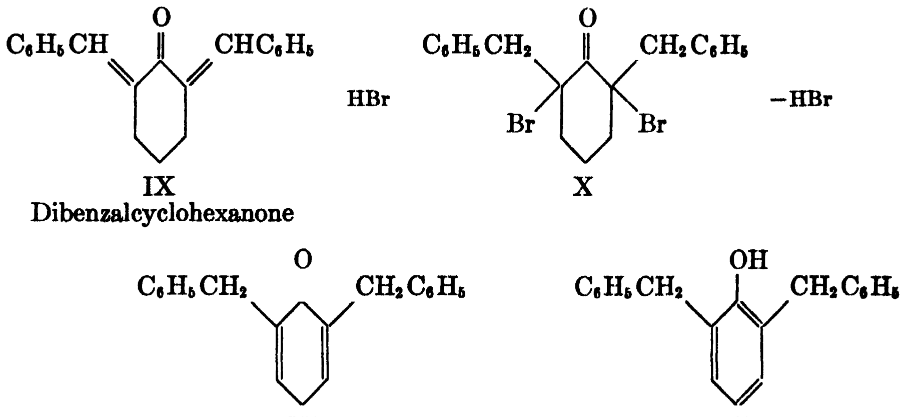


VII
Carvacrylamine



VIII

An interesting rearrangement is that described by Weiss and Ebert (138), who obtained 2,6-dibenzylphenol (XII) in the form of its acetate from treatment of dibenzalcyclohexanone (IX) with a solution of hydrogen bromide in acetic acid



IX
Dibenzalcyclohexanone

X

XI

XII
2,6-Dibenzylphenol

and acetic anhydride at 52–55°C. There is postulated an intermediate X which undergoes dehydrohalogenation to XI, which then isomerizes.

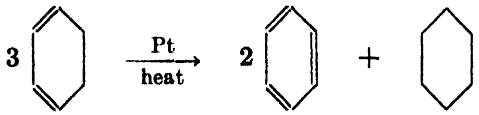
A consideration of the experimental conditions capable of inducing isomerization of the compounds presented here, together with a number of those noted later, indicates that in cases where the isomerization takes place very readily apparently all that is required is an acid environment, the nature of the acid being immaterial. In such cases the rearrangement probably proceeds through an ionic intermediate. Solutions of hydrogen chloride or hydrogen bromide in acetic acid are agents capable of inducing isomerization in a wide variety of instances, and in a number of these cases the alicyclic isomers are not susceptible to isomerization by simple contact with an acid medium. Unfortunately the limitations of this mode of aromatization, as a general method, have never been determined, and it is therefore impossible to estimate the range of usefulness of the method.

3. Catalytic

A method of aromatization which is both convenient and quite general in its usefulness lies in the use of catalysts of the hydrogenation group. These catalysts are capable of directing their action on portions of bond systems which show unsaturation, and their investigation in connection with this type of isomerization is therefore indicated.

Wallach, in his studies of the hydrogenation of carvone with a palladium catalyst under the usual mild conditions, found that carvacrol was always one of the products (136). Linstead encountered the same difficulty in reducing carvone to carvomenthone, and it was found in separate experiments that a slow isomerization of carvone will proceed at room temperature over the catalyst (80). Similarly, Wallach found that carvone oxime (V), when hydrogenated with the palladium catalyst of Paal, gave always some carvacrylamine (VII) (135). The latter again is probably formed from the hydroxylamine (VI) by reduction.

The effect of hydrogenation catalysts upon bond systems is a problem which has been developed very rapidly within recent years. The work of Linstead (79, 80, 81, 82) on the use of noble metals in dehydrogenations and disproportionations, and the dehydrogenation studies of Adkins (1, 2, 3, 103) indicate that hydrogenation catalysts have the ability to transfer hydrogen from one organic molecule to another, or simply to add and/or remove hydrogen from certain structures, with or without the aid of molecular hydrogen.[6] It is required here, however, to transform an unsaturated compound into another at the same formal level of unsaturation; there is no specific hydrogenation or dehydrogenation involved, and such a process may apparently also proceed without the intervention of molecular hydrogen. If only two molecular species are involved, the reaction is one of isomeric aromatization (or *intramolecular* disproportionation); if three or more species are involved, the reaction is one of (*intermolecular*) disproportionation or irreversible catalysis (the latter term was used by Zelinsky, and Russian workers have retained this designation). The difference between these two types of reactions, so far as the intimate mechanism is concerned, is not well defined, and it is quite possible that in some or all cases the mechanism is the same. For example, a typical disproportionation is the conversion of 1,3-cyclohexadiene into a mixture of benzene and cyclohexane through the agency of a platinum catalyst (78):



Cyclohexadiene Benzene Cyclohexane

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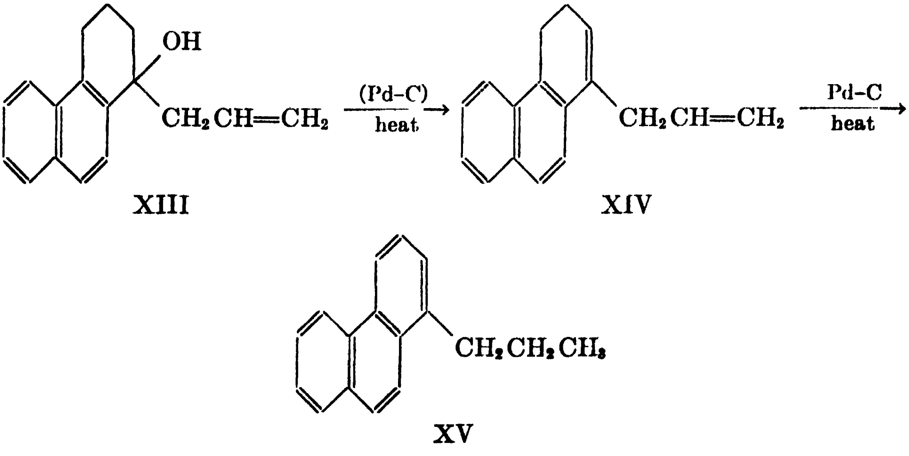
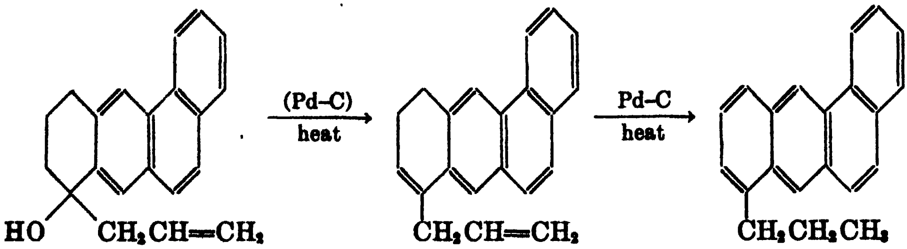
[6] See also Taylor (J. Am. Chem. Soc. **60**, 627 (1938)) for a discussion of dehydrogenation, particularly with respect to the Balandin multiplet theory, and Levina (J. Gen. Chem. (U.S.S.R.) **4**, 1250 (1934); **6**, 764, 1092, 1496 (1936); **7**, 353, 402, 747, 1587, 1866 (1937); **8**, 1776 (1938); **9**, 825, 1834, 2287 (1939); **10**, 913 (1940); **11**, 527, 533 (1941); **12**, 422 (1942)) for an extensive study of isomerizations and disproportionations (irreversible catalysis).

This reaction involves the transference of hydrogen atoms from one molecule of cyclohexadiene to another, the net result being the formation of benzene and cyclohexane. This process may involve a dehydrogenation on the catalyst surface, followed by desorption of the benzene molecule which is formed, but not of the hydrogen. The next cyclohexadiene molecule to be adsorbed is then hydrogenated instead of being dehydrogenated. Such a process requires the successive adsorption of cyclohexadiene molecules without desorption of hydrogen, and is essentially a two-stage process. A successive-stage process of this type could also be assumed for intramolecular disproportionation, but it is also possible that the isomerization mechanism involves a rearrangement which takes place on the catalyst surface, and that only a single adsorption is required for each rearrangement. In this case the hydrogen is merely transferred from one part of the molecule to another, and there is no intermolecular action.

In any event, the effectiveness with which the isomerization can be carried out is dependent chiefly upon the nature of the catalyst. That a palladium catalyst is active in this respect even at room temperature, although the rate of aromatization is slow, has already been noted. At elevated temperatures with the same catalyst the reaction proceeds smoothly and rapidly. Linstead (80) heated carvone at temperatures in the range 20–230°C. for varying lengths of time with a palladium–charcoal catalyst in an atmosphere of carbon dioxide. Treatment for 12 hr. at 230°C. yielded 95 per cent of carvacrol, and 2 hr. at 228°C. 81 per cent of carvacrol. Bachmann has employed this method for synthetic purposes in several instances: the conversion of the alcohols XIII and XVI to the hydrocarbons XV and XVIII (8, 10) by heating with a palladium–charcoal catalyst evidently proceeds by way of the alicyclic intermediates XIV and XVII.

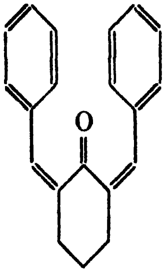
In this connection it is interesting to note a rather unusual experiment (41) in which dibenzalcyclohexanone (XIX) and dianisalcyclohexanone (XXI) were converted into the corresponding phenols (XX, XXII) in excellent yields. The alicyclic compounds were treated with hydrogen and a palladium catalyst at a temperature of 200–250°C., and after hydrogenation was complete the tempera-



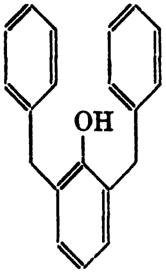


XVI XVII XVIII

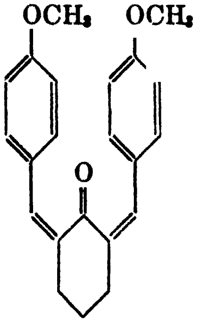
ture was raised to 325–330°C. to effect dehydrogenation. This procedure involves two steps of directly opposite natures. It should be possible to omit the hydrogen and attain the same result.



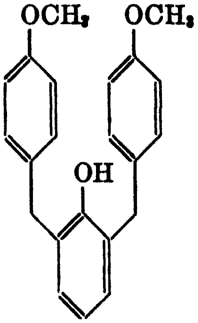
XIX
Dibenzalcyclohexanone



XX



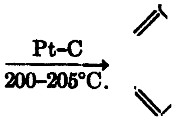
XXI
Dianisalcyclohexanone



XXII

Platinum catalysts are employed less frequently than palladium catalysts for dehydrogenations, although there is little difference in the activity of the two in this connection. It is therefore likely that isomeric aromatizations can also be induced by platinum catalysts, but there are very few observations in support of this view. One interesting rearrangement which involves the use of a platinum–charcoal catalyst is the isomerization of the enyne XXIII to ethylbenzene (XXIV) (77). The acetylene bond group provides the equivalent of two double bonds.

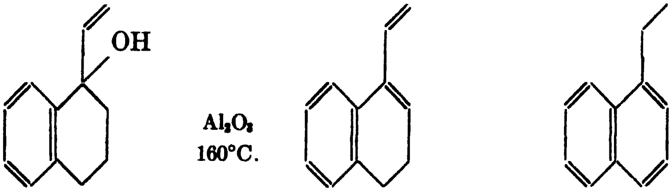
Raney nickel has proved useful in establishing an equilibrium in certain cases of isomerism. For example, Cope (27) found that an equilibrium between the



XXIII XXIV
Ethylbenzene

α,β- and β,γ-forms of several unsaturated (olefinic) esters could be established by heating the esters with Raney nickel at 180°C. Nickel supported on kieselguhr, chromium oxide, or alumina has been employed in dehydrogenation studies (usually at elevated temperatures and pressures) by Adkins (1). There are, however, no general observations available on the activity of nickel catalysts in inducing isomeric aromatizations.

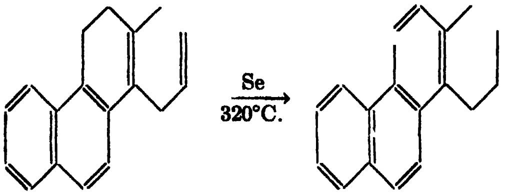
Activated alumina is effective in establishing certain types of isomeric conversion involving unsaturated compounds. For example, isomerization equilibria among the branched-chain pentenes (40) and among dienes (56) have been investigated, employing activated alumina at relatively high temperatures. Observations of isomeric aromatization over alumina are rare, but one such example seems to be the reaction described by Goldberg (50) in which the tertiary alcohol XXV was passed over alumina at 160°C. The product was not the expected vinyldihydronaphthalene (XXVI) but the isomeric compound, α-ethylnaphthalene (XXVII).



XXV XXVI XXVII
α-Ethylnaphthalene

Sulfur and selenium are not ordinarily regarded as dehydrogenation catalysts, but they are capable of dehydrogenating a wide variety of alicyclic molecules to yield aromatic structures. The hydrogen is eliminated as hydrogen sulfide or hydrogen selenide, and this particular process has never been carried out in the reverse direction. Selenium, however, is capable of acting as a hydrogenation catalyst, although its activity in this respect is very low, and it also has the ability to induce isomeric aromatization. This was demonstrated by Cook's studies (24) of the hydrocarbon XXVIII. The rearrangement to the aromatic isomer XXIX was effected by heating with selenium at 320°C. for 15 hr. It was also found possible to effect the isomerization by heating for 1 hr. in acetic acid saturated with hydrogen chloride, but boiling formic acid was without action.

These examples demonstrate the possibility of the occurrence of isomeric aromatization under certain definite circumstances. Comparatively little is known as to the limitations of the methods for inducing such rearrangements, but the two most useful agents seem to be solutions of hydrogen bromide or hydrogen chloride in acetic acid, and palladium–charcoal catalysts.

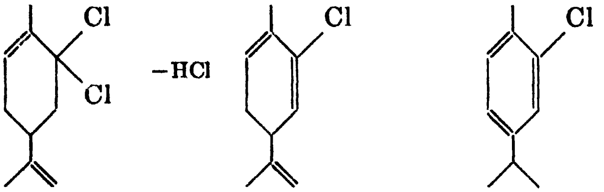


XXVIII XXIX

C. ISOMERIZATIONS INVOLVING CARBON–CARBON BONDS ONLY

1. *Benzene derivatives*

(*a*) *One exocyclic bond:* The unsaturated hydrocarbons derived from carvone through the Grignard reaction have been mentioned previously (page 110); their rearrangement takes place readily. The corresponding isoamyl compound (R = $i\text{-}C_5H_{11}$) has been prepared (117, 118) but its aromatization has not been described. A related compound is the dichloride (I) obtained from carvone and phosphorus pentachloride. Boiling in quinoline yields 2-chlorocymene (III) (65) by way of the alicyclic compound II.



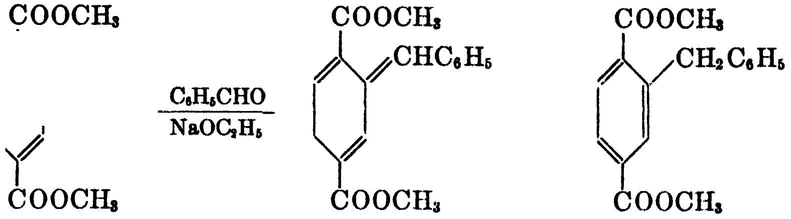
II III
2-Chlorocymene

Dehydroperillic acid (IV), an alicyclic acid occurring in the western red cedar, is transformed by contact with hydrochloric acid (in acetic acid) into the isomeric aromatic acid, cuminic acid (V) (4).

IV
Dehydroperillic acid

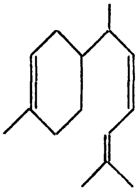
V
Cuminic acid

The methyl ester of $\Delta^{1,4}$-dihydroterephthalic acid will undergo condensation with aromatic aldehydes, such as benzaldehyde, to yield a diphenylmethane derivative (VII) (123). The intermediate (VI) rearranges immediately after formation to the aromatic isomer (VII).

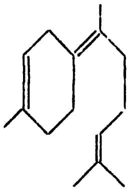


VI VII

(*b*) *Two exocyclic bonds:* Compounds such as zingiberene (VIII) and bisabolene (IX) fall into this class, but no record of rearrangements of these compounds to the corresponding alkylbenzenes has been found. Subjection of both compounds to conditions which might be expected to lead to isomeric aromatization results instead in ring closure to a hydrogenated cadalene. Dehydrogenation conditions lead to cadalene, owing to this ring closure (106).



VIII
Zingiberene

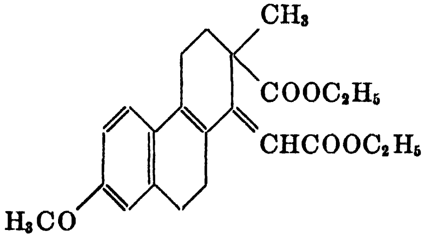


IX
Bisabolene

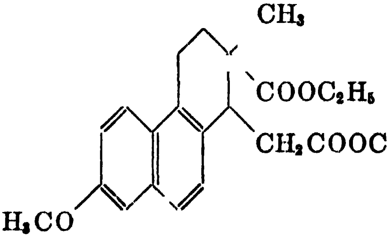
(*c*) *Three exocyclic bonds:* No examples in this class have been found.

2. Naphthalene derivatives

(*a*) *One exocyclic bond:* An example in this group is the rearrangement of vinyldihydronaphthalene previously cited (50). Another example is the isomerization carried out by Bachmann, Kushner, and Stevenson (9) in which the ester X was converted into its aromatic isomer, XI, by heating with a palladium-charcoal catalyst.



X

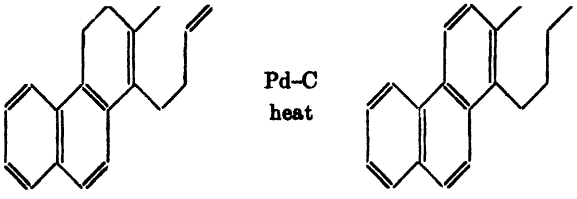


XI

(*b*) *Two or more exocyclic bonds:* No examples in this group have been found.

3. *Polynuclear derivatives*

The rearrangements carried out by Bachmann (8, 10), which have been noted earlier (page 113), are examples in this class. Another such rearrangement is the transformation of the hydrocarbon XII into its aromatic isomer XIII by heating with a palladium–charcoal catalyst (21).

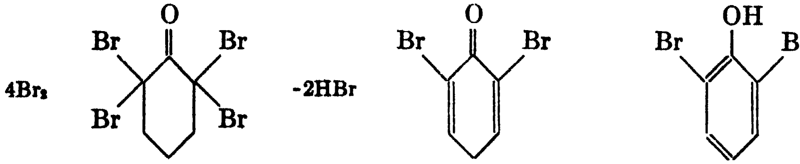


XII XIII

D. ISOMERIZATIONS INVOLVING CARBON–OXYGEN BONDS

1. *Benzene derivatives*

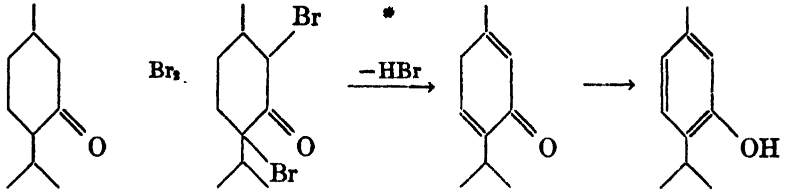
(*a*) *One exocyclic bond:* This group includes a number of rearrangements of intermediate compounds in certain bromination methods which have been employed for the preparation of phenols. The method in general (12) consists of the preparation of a halogen-containing derivative of a hydroaromatic ketone, followed by dehydrohalogenation to yield an aromatic compound. The halogen, which is usually bromine, may be introduced either by substitution or by addition, and the second step in the reaction is usually accomplished by boiling with a tertiary amine such as dimethylaniline or quinoline, or in some cases simply by heating. The yields vary, but are usually in the range 40 to 60 per cent. For example, cyclohexanone (I) will form a tetrabromo derivative (II) which may be converted into 2,6-dibromophenol (IV) (134); the intermediate which aromatizes is undoubtedly III. A similar series of steps will convert menthone (V) into thymol (VIII) (14) by way of the dibromide (VI). The intermediate which isomerizes is probably VII. In each case the rearrangement occurs at once; the expected intermediates (III and VII) have no more than a transient existence.



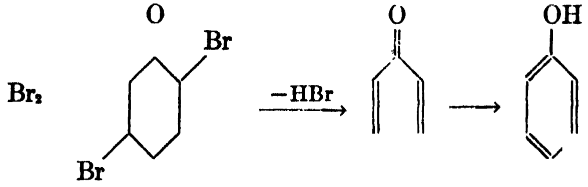
II III IV

Cyclohexanone 2,6-Dibromophenol

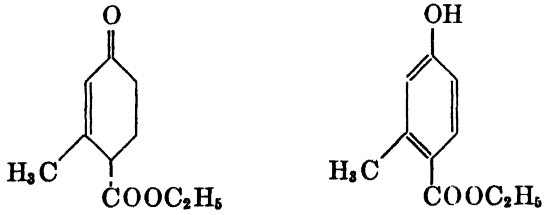
Δ^2-Cyclohexenones may also be aromatized by this method. Presumably the bromine adds in 1,4-fashion to the enol form; dehydrohalogenation can usually be effected easily and the product is the corresponding phenol. This process has been carried out with cyclohexenone (IX) to yield phenol (X) (70), and with a number of cyclohexenones derived from the bis-esters obtained from acetoacetic ester and aldehydes through the Knoevenagel condensation. The phenolic esters XI (102) and XII (67) have been obtained in this fashion. Also, a number of disubstituted phenols (XIII) in which R is an aliphatic radical or hydrogen have been prepared in the same way (68). The general nature of the latter



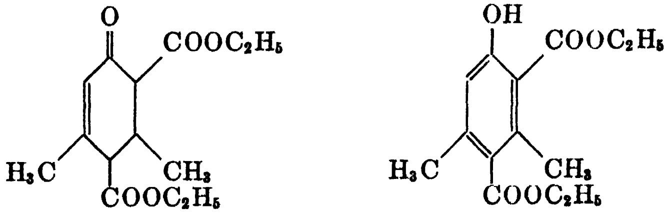
V Menthone VI VII VIII Thymol



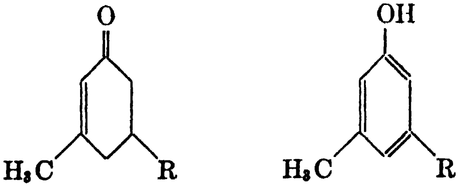
IX Cyclohexenone X Phenol



XI



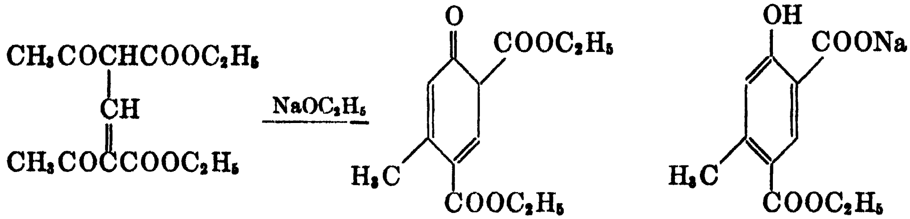
XII



XIII

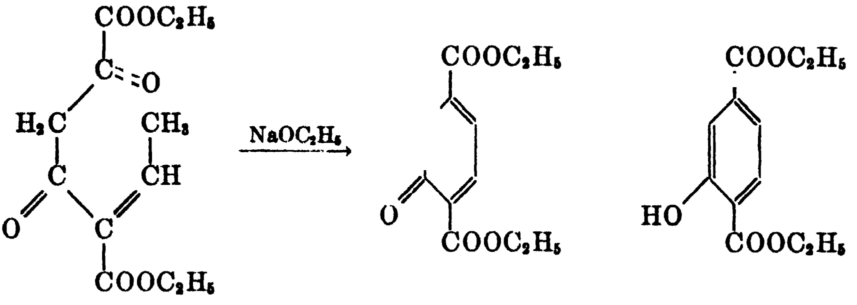
reaction has been studied by Petrov (97) and extended to include aromatic substituents.

There are also several ring-closure reactions which lead to compounds in this group. From ethyl orthoformate and acetoacetic ester there may be obtained ethyl ethoxymethyleneacetoacetate, which will undergo further reaction with ethyl acetoacetate to yield the diester XIV. Under the influence of sodium ethoxide a ring closure occurs to yield the intermediate XV. This is followed by isomerization and partial saponification of the resulting phenolic ester. The sequence of steps is shown; the product is XVI (23). The reaction may be modified by replacement of the orthoformic ester by related compounds like chloroform or chloral (94, 95).



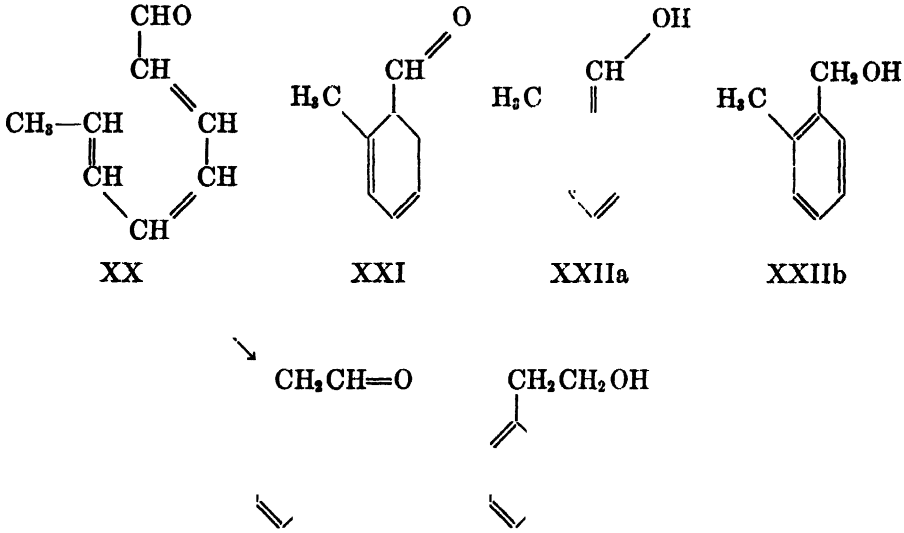
XIV XV XVI

The same ring structure is present in the intermediate (XVIII) presumably obtained from the action of sodium ethoxide on ethyl α-ethylidene-γ-ethoxalylacetoacetate (XVII). The isomerization occurs immediately under the reaction conditions and the product is the hydroxyterephthalic ester XIX (113).



XVII XVIII XIX

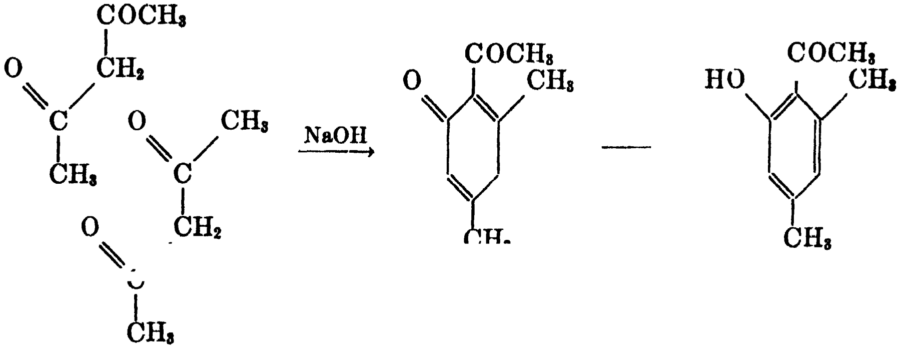
A compound whose reported structure is remarkable in that its isomerization was not observed is the aldehyde XXI. The unsaturated aldehyde XX may be obtained from the self-condensation of crotonaldehyde, and it will itself undergo further reaction through intramolecular addition to yield a cyclic unsaturated aldehyde to which the structure XXI has been assigned. The rearrangement of this compound should take place with great ease, since enolization would provide a hydroxymethylenedihydrobenzene (XXIIa), and this structure would undoubtedly instantly isomerize to the benzyl alcohol XXIIb. An alternative formulation for the intramolecular addition is that of a Michael vinylog leading to the dihydrobenzene XXIII. This compound (XXIII) should be more stable with respect to rearrangement (to β-phenylethyl alcohol, XXIV) than the dihydrobenzene XXI. The investigators of the reaction, however, have obtained evidence indicating that XXI is the reaction product (15).



XX XXI XXIIa XXIIb

XXIII XXIV

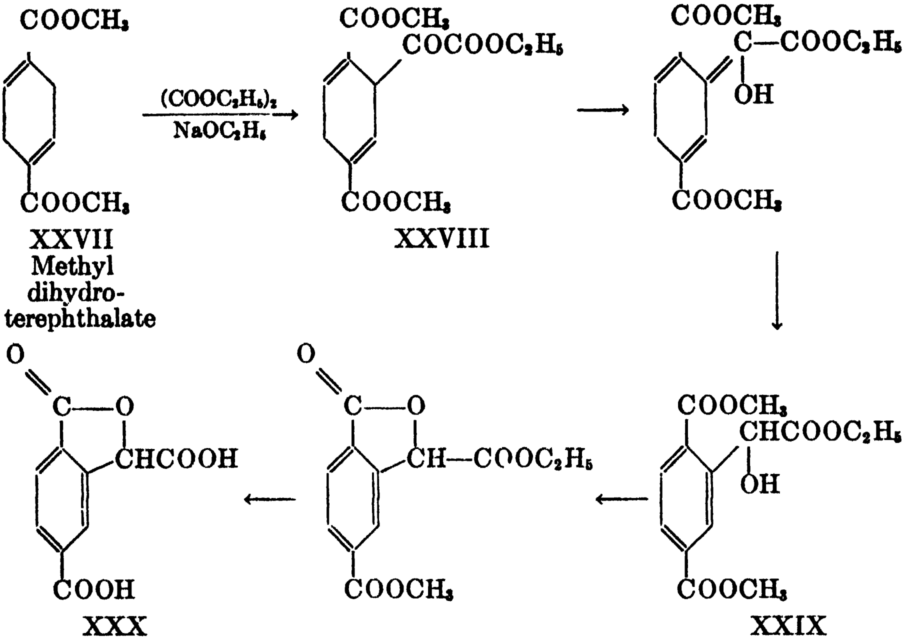
A somewhat different condensation is the reaction of acetylacetone (XXV) with itself under the influence of sodium hydroxide, the product being the hydroxyacetophenone XXVI (55).



XXV
Acetylacetone

XXVI

The condensation of methyl dihydroterephthalate with benzaldehyde has been noted previously. The ester (XXVII) will also react with ethyl oxalate in the presence of sodium ethoxide. The product is not the glyoxalate (XXVIII), however, since the latter immediately isomerizes to a benzyl alcohol derivative



XXVII Methyl dihydroterephthalate

XXVIII

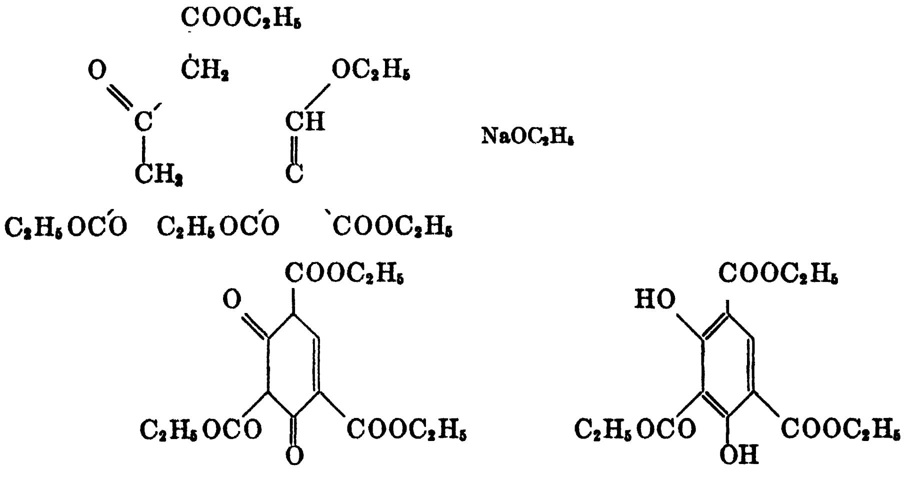
XXIX

XXX

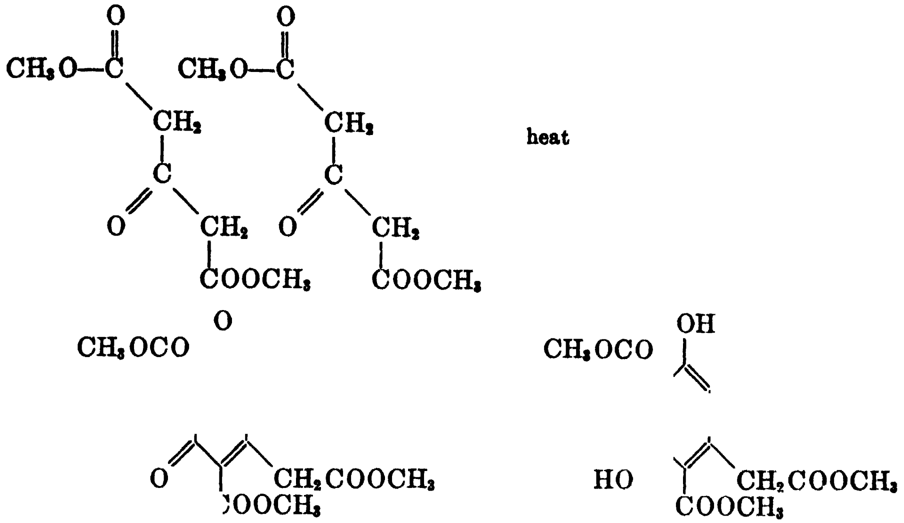
(XXIX). Lactonization then occurs, and saponification results in the lactonic acid XXX (123).

(*b*) *Two exocyclic bonds:* The rearrangement of carvone should be included here. The circumstances under which it aromatizes have been noted previously.

Two condensations affording compounds in this group which isomerize



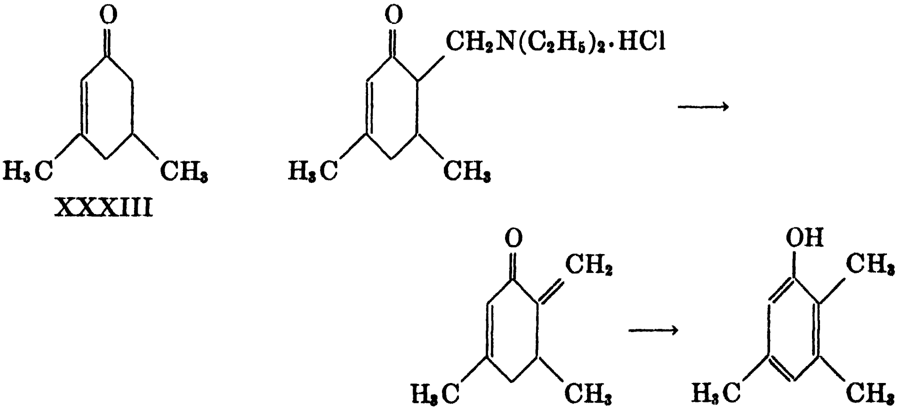
XXXI



XXXII

immediately are those described by Errera (XXXI) (39) and Dootson (XXXII) (31).

The Δ²-cyclohexenones of Knoevenagel may be employed for the production of certain trisubstituted phenols. For example, 3,5-dimethyl-Δ²-cyclohexenone (XXXIII) may be carried through a Mannich reaction to yield an amine hydrochloride from whose pyrolysis there may be obtained 2,3,5-trimethylphenol (XXXV) (58). The probable mechanism is as shown:



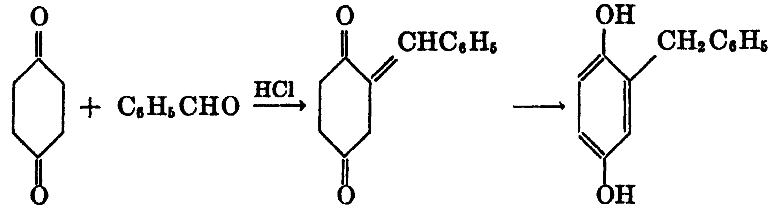
XXXIII

XXXIV

XXXV
2,3,5-Trimethylphenol

(*c*) *Three exocyclic bonds:* The condensation of benzaldehyde with cyclohexanone to dibenzalcyclohexanone and the rearrangement of the latter to 2,6-dibenzylphenol have been noted. If benzaldehyde is condensed with 1,4-

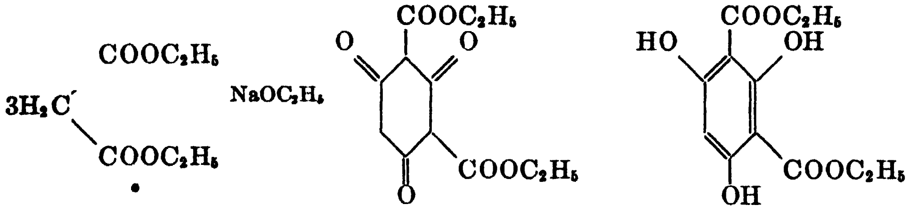
cyclohexanedione (XXXVI) the two keto oxygen atoms are transformed into phenolic oxygens and the product is benzylhydroquinone (XXXVII) (120).



XXXVI
1,4-Cyclohexanedione

XXXVII
Benzylhydroquinone

The self-condensation of malonic ester (XXXVIII) (76, 91) may result in a phloroglucinol derivative (XL), the reaction passing through the corresponding tautomeric intermediate (XXXIX).



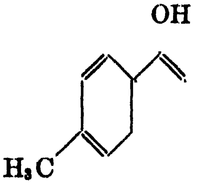
XXXVIII
Malonic ester

XXXIX

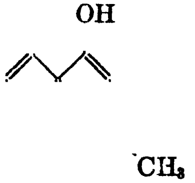
XL

2. *Naphthalene derivatives*

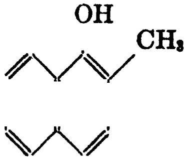
(*a*) *One exocyclic bond:* This group includes the intermediates in those reactions in which the bromination method of aromatization is employed to convert tetralones into naphthols. Naphthols such as XLI (43), XLIIa and XLIIb (125), and XLIII (75) have been prepared from the corresponding α-tetralones by this process. One bromine atom is introduced in the 2-position by a substitution reaction, and dehydrohalogenation accompanied by isomerization then yields the naphthols. For example:



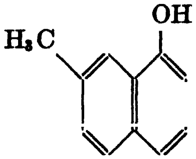
XLI



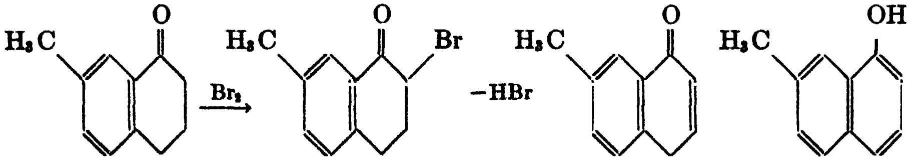
XLIIa



XLIIb

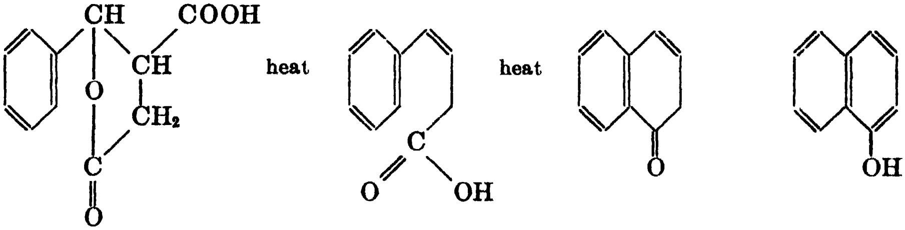


XLIII

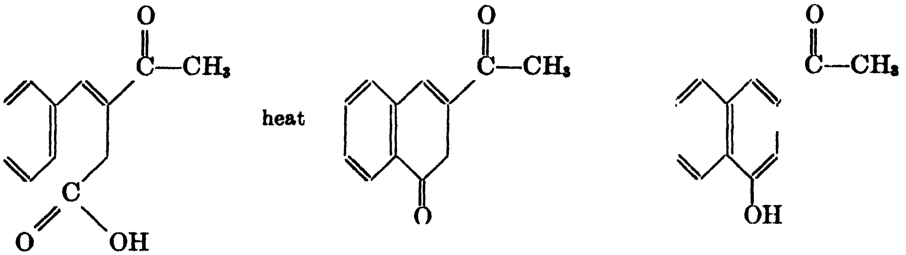


XLIII

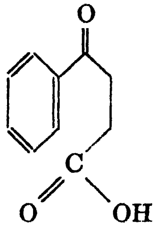
This group also includes compounds intermediate in two interesting series of ring-closure reactions, the Fittig condensation and the condensation of Menon. Both lead to α-naphthols, but the intermediates involved are different. The Fittig condensation requires the ring closure, under the influence of heat, of an unsaturated acid of the basic structure XLV to a ketonic intermediate (XLVI) which immediately aromatizes to the corresponding α-naphthol (XLVII). It was found by Fittig that the product of the Perkin condensation of benzaldehyde and succinic anhydride, phenylparaconic acid (XLIV), decomposed on heating to form the simplest of such acids, β-benzalpropionic acid (XLV) (47). The observation was then made that further heating (distillation) of the unsaturated acid caused its conversion into α-naphthol (46). The synthesis was later extended to 3-methyl-1-naphthol (48) and to chlorinated naphthols (37, 38). The same basic structure is present in β-benzallevulinic acid (XLVIII), and the transformation of this compound into 3-acetyl-1-naphthol (XLIX) by the same route has been described by Erdmann (36).



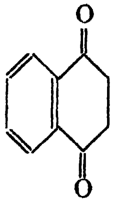
XLIV Phenylparaconic acid XLV β-Benzalpropionic acid XLVI XLVII α-Naphthol

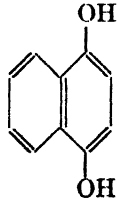


XLVIII β-Benzallevulinic acid XLIX 3-Acetyl-1-naphthol



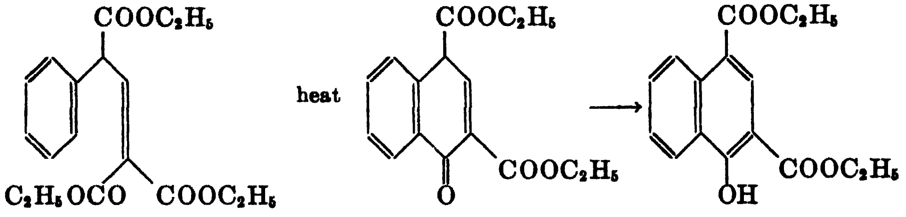
L



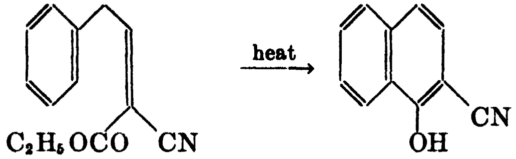


It may be of interest to point out that an attempt to cyclize the keto acid L by analogy with the Fittig reaction was unsuccessful (13).

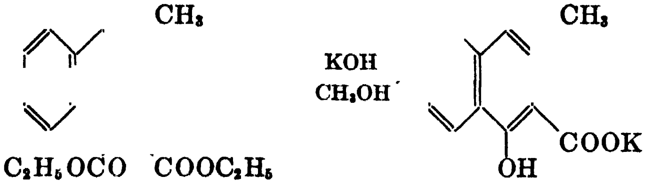
A related condensation may be carried out with certain unsaturated esters. It was found by Menon (87) that the ester LI on heating was converted into the naphthol LIII, the intermediate being as shown (LII). Other examples of this type of condensation leading to LIV, LV, and LVI were found by McRae and Marion (85, 86). The ring closure to LVI was also encountered by Cope (28), who found that the reaction proceeded smoothly in the presence of acetamide at 200–220°C.



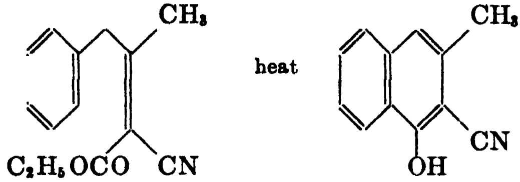
LI LII LIII



LIV



LV

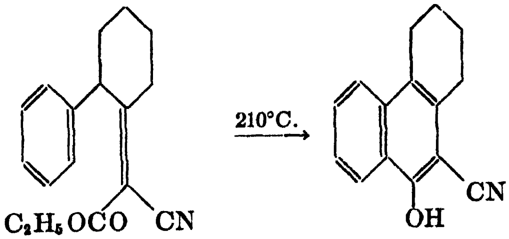


LVI

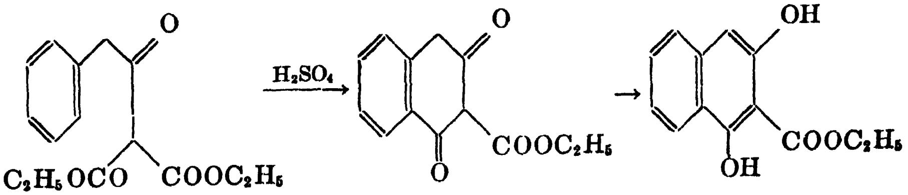
Another ring closure of this type was found by Linstead to occur when the ester LVII was heated, the product being LVIII (83).

(*b*) *Two exocyclic bonds:* In this group are compounds resulting from a type of ring closure related to that just described. The keto esters LIX and LXII will undergo ring closure in concentrated sulfuric acid to yield the naphthols LXI (89) and LXIV (129); the probable alicyclic intermediates are as shown (LX and LXIII).

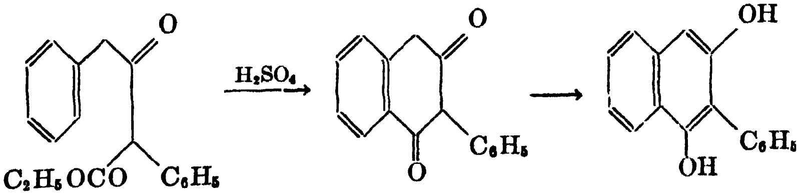
A 1,4-diketone isomeric with a naphthohydroquinone results from the Claisen condensation of ethyl phthalate and ethyl succinate, a reaction recently de-



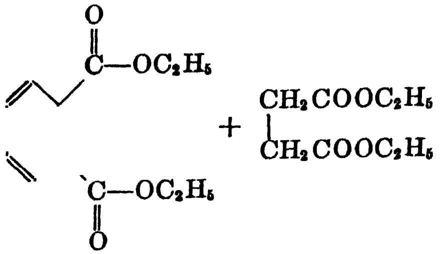
LVII LVIII



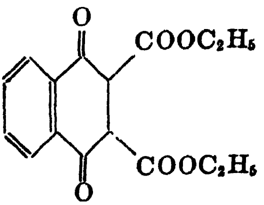
LIX LX LXI



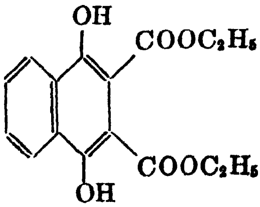
LXII LXIII LXIV



Ethyl phthalate Ethyl succinate



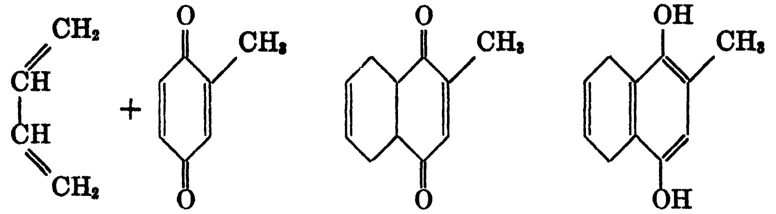
LXV



LXVI

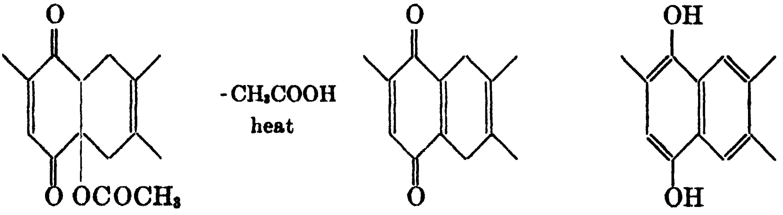
scribed by Homeyer and Wallingford (57). The normally expected product (LXV) rearranged at once under the reaction conditions to the corresponding naphthol (LXVI).

The 1,4-diketo system is also present in a number of dihydronaphthalene isomers which may be obtained from the Diels–Alder addition of benzoquinones and butadiene (44, 45). For example, toluquinone and butadiene will undergo addition to yield the diketone LXVII. This is an alicyclic isomer of the dihydronaphthohydroquinone LXVIII, and its isomeric aromatization to the latter may be effected simply by adding a little hydrochloric acid to an ethanol solution of the diketone. Stannous chloride is usually also added to protect the resulting hydroquinone against oxidation. In general, the rearrangement of these compounds will take place under the influence of traces of either acids or bases. (This reaction involves aromatization to a benzene ring rather than to the naphthalene structure, but is placed here because it is used for the preparation of 1,4-naphthohydroquinones.)



Butadiene Toluquinone LXVII LXVIII

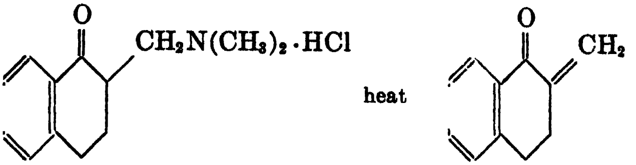
A similar type of intermediate, but one which in this case has no more than a hypothetical existence, results from the thermally induced expulsion of acetic acid from the diketoalcohol acetate LXIX (22). The reaction product is the 1,4-naphthohydroquinone (LXXI) isomeric with the normally expected alicyclic diketone LXX.



LXIX LXX LXXI

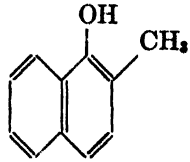
A product of the Mannich reaction with α-tetralone is the ketoamine hydrochloride LXXII. Deamination results in the *o*-methyleneketone LXXIII. This compound is an alicyclic isomer of β-methyl-α-naphthol (LXXIV) and may be isomerized to the latter (59). The intermediate here (LXXIII) has a longer life under similar conditions than benzene analogs, and when allowed to stand the tendency to dimerize is apparently greater than the tendency to isomerize.

The compound reported a few years ago (62) as β-methylene-α-tetralone (LXXIII) does not have this structure, but is a dimer (59).



LXXII

LXXIII
β-Methylene-α-tetralone

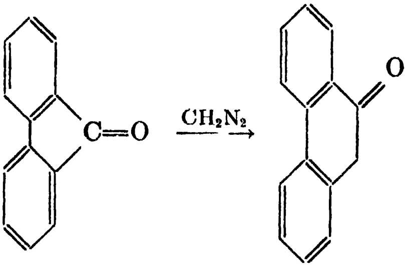


LXXIV
β-Methyl-
α-naphthol

3. *Polynuclear derivatives*

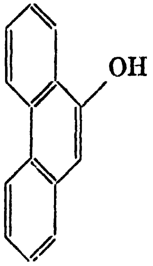
An example is found in the production of a phenanthrol from the corresponding tetralone-like compound by the bromination method (92). The method follows that described for phenols and naphthols.

The ring-expanding effect of diazomethane when applied to alicyclic ketones can also be extended to aromatic ketones. Fluorenone (LXXV) when treated with diazomethane should provide an intermediate of structure LXXVI. The product of the reaction is actually the aromatic isomer, 9-phenanthrol (LXXVII), principally as the methyl ether (114).



LXXV
Fluorenone

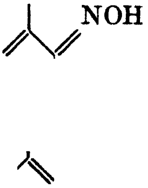
LXXVI



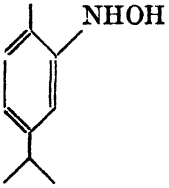
LXXVII
9-Phenanthrol

E. ISOMERIZATIONS INVOLVING CARBON—NITROGEN BONDS

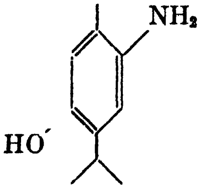
Very few such rearrangements are to be found in the literature, although the method offers a potential source of some unusual hydroxylamines and amines. Carvone oxime (I) has been mentioned previously, and another reaction of this oxime which definitely demonstrates its mode of isomerization is the formation of the p-aminophenol III through the action of sulfuric acid on the oxime (133).



I
Carvone oxime



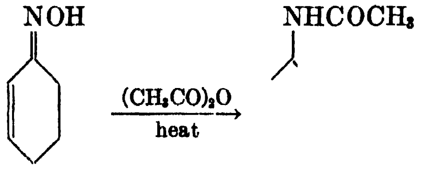
II



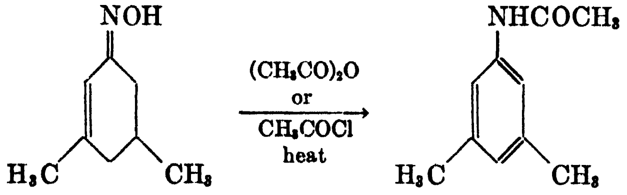
III

The intermediate is the hydroxylamine (II) isomeric with the oxime, and the *p*-aminophenol (III) derives from this hydroxylamine by the usual rearrangement of such compounds.

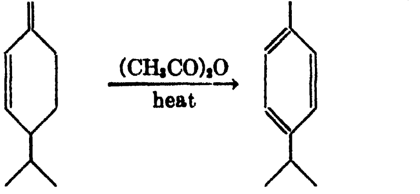
A reaction which may require inclusion at this point is Wolff's method for the conversion of oximes to amines. The oximes of certain cyclohexenones are converted to amines (in the form of the hydrochloride or the aceto derivative) by heating with such agents as hydrochloric acid, acetic anhydride, or acetyl chloride. The reaction conditions suggest a dehydration, followed by rearrangement, but it is difficult to describe the intermediate. The normal dehydration of an oxime to a nitrile is denied by the preservation of the ring structure which includes the oxime carbon atom. The simplest such rearrangement is that of Δ^2-cyclohexenone oxime (IV) (71); another is that of the oxime of 3,5-dimethyl-Δ^2-cyclohexenone (V) (144). The same reaction was found by Macbeth (26) to occur with the oxime VI. Piperitone oxime (VII) and carvone oxime (I) underwent the reaction much less readily.



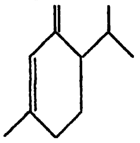
IV



V

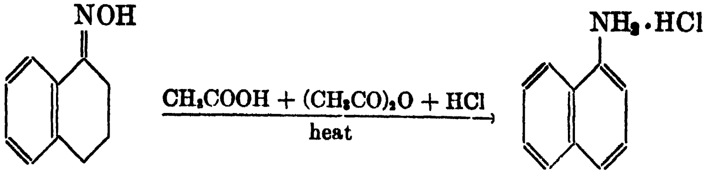


VI



VII
Piperitone oxime

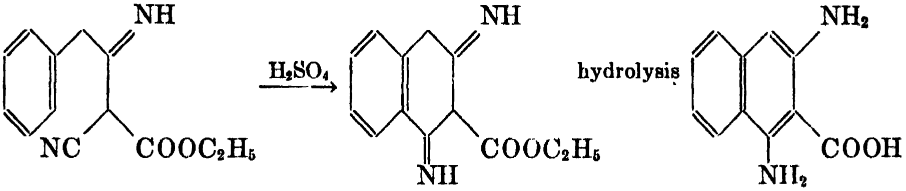
The same type of reaction, applied this time to α-tetralone and substituted α-tetralone oximes, was investigated by Schroeter (112). A number of α-naphthylamines were obtained, the general reaction being:



VIII
α-Naphthylamine hydrochloride

This reaction was usually carried out in an acetic acid–acetic anhydride solution containing hydrogen chloride; the product was then the naphthylamine hydrochloride (VIII). The explanation of the mechanism involved a "Lücken-molekül" as the intermediate. It was found that ortho-substitution led to a Beckmann rearrangement instead of to aromatization.

It was found by Thorpe (6) that the imino-nitrile-ester IX would undergo ring closure under the influence of sulfuric acid. The result of the ring closure was doubtless compound X, a diimine isomeric with the corresponding naphthalenic diamine, but the reaction product on hydrolysis was actually the amino acid XI. The reaction was also carried out by the same author for a number of analogs (6, 16).



IX XI

IV. Summary

This review has been designed to correlate and classify reactions in the literature which involve alicyclic–aromatic isomerizations. There are doubtless many which have escaped detection, since examples frequently occur in association with larger pieces of work to which they are only incidental. This type of isomerization has received less attention than is its due. It represents a connecting link between alicyclic and aromatic compounds, and in this capacity it may provide information useful in exploring the structure and reactions of many members of both classes. Together with dehydrogenation methods, it also presents a practical synthetic approach to aromatic compounds which is primarily dependent upon aliphatic or alicyclic compounds and reactions. The limitations of these two methods are chiefly those of aliphatic or alicyclic chemistry rather than the limitations imposed by the laws of aromatic substitution. Dehydrogenation methods have been widely used in the preparation of aromatic hydrocarbons, but are less applicable to the preparation of compounds in other functional classes. Isomerization methods appear to be particularly suited to the preparation of hydrocarbons, phenols, and amines (or hydroxylamines).

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THE STEREOCHEMISTRY OF SQUARE COMPLEXES[1]

DAVID P. MELLOR

Department of Chemistry, University of Sydney, New South Wales

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Traditional chemical methods of unravelling questions of molecular structure fail to provide a unique solution to the problem of the structure of bivalent platinum compounds. The various alternative configurations which may be used to explain the phenomena of geometrical and mirror-image isomerism among platinous complexes can be successively narrowed down by different chemical and physical methods of investigation until but one possibility remains—namely, square coördination. The theory of square coördination makes possible the correlation and interpretation of such a large mass of data on the compounds of bivalent platinum and certain other metals that there can be no reasonable doubt of the reality of this type of structure. With the reservation that it applies only to bonds free to arrange, the theory of the directed valence bond makes it clear just what metal atoms are likely to form square bonds.

I. INTRODUCTION

In the design of molecules Nature uses relatively few fundamental units of pattern or configurations, and it is naturally important to know what these are and under what circumstances any particular configuration is likely to be found. We shall here be concerned with the narrow field of stereochemistry which deals with the orientation in space of the four valence bonds of quadricovalent elements. The tetrahedral disposition of four valence bonds about the carbon atom was the first configuration to be discovered, and so widespread did its occurrence eventually prove to be, not only among the compounds of carbon, where it was universal, but also among some forty other elements, that attention to this type of structure long overshadowed that given to an alternative arrangement of four bonds in space—namely, the square arrangement. Indeed, the tetrahedral arrangement proved to be so dominant a feature of molecular architecture that the very existence of the square pattern was,—and, for that matter, in some quarters still is,—a matter of controversy. Nevertheless the evidence on this question has grown steadily over the last few years and the time is opportune for some attempt to evaluate the significance of the square configuration for the stereochemistry of the metals.

In attempting to do this, two main questions will be considered: firstly, how strong is the evidence for the square disposition of valence bonds, and secondly, with what elements and under what circumstances does it occur? In tracing the developments leading to the proof of square coördination, attention will be centered on the compounds of platinous platinum (Pt^{II}), because it is with these that the most abundant and satisfactory evidence has been obtained. Notwithstanding this, there has been a good deal of controversy about the structure of platinum compounds. Some idea of the controversial nature of this field may be gathered from a few excerpts, chosen at random, from the recent literature:

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[1] This article is based largely on the Presidential Address to the Royal Society of New South Wales, April 1, 1942.

> "Platinum salts combine with an enormous number of inorganic and organic groups or molecules and many of these salts have been known for a hundred years, yet the constitution of the isomeric diammines of the type $[PtA_2X_2]$ is still a subject of controversy" (17).
>
> "It is still an open question whether the experimental work (relating to planar and tetrahedral structures) has been correctly interpreted or not or whether some elements can assume more than one structure" (5).
>
> "In any event, the problem presented by these salts (certain allegedly optically active platinous salts) does not seem to be finally cleared up" (135).

Although, in a certain sense, no scientific problem is ever cleared up, there is reason to believe that the main outlines of the stereochemistry of bivalent platinum are well established and it is hoped to show that the issues raised in these quotations have now been largely settled.

II. THE DISCOVERY OF THE SQUARE CONFIGURATION

It is not surprising that the square configuration was first discovered among the compounds of Pt^{II}, because, as we now know, no other element forms so many compounds which exhibit isomerism on account of this stereochemical characteristic. The two substances primarily concerned with the development of our knowledge in this field,—namely, the α- and β-forms of dichlorodiammineplatinum, $[Pt(NH_3)_2Cl_2]$,—were discovered nearly a century ago, the former by Peyrone (123) and the latter by Reiset (133).[2]

The methods used in their preparation involve two similar processes; the α-compound is made by replacing two chlorine atoms of the $[PtCl_4]^{--}$ ion with ammonia molecules, the β-form by replacing two ammonia molecules of the $[Pt(NH_3)_4]^{++}$ ion with chlorine atoms. The latter operation is effected either by heating solid $[Pt(NH_3)_4]Cl_2$ under carefully controlled conditions or by treating the aqueous solution with concentrated hydrochloric acid; the former, by treating K_2PtCl_4 with aqueous ammonia. There is little doubt that each of the above substitutions proceeds stepwise:

$$[PtCl_4]^{--} \xrightarrow{NH_3} [Pt(NH_3)Cl_3]^{-} \xrightarrow{NH_3} \underset{\alpha}{[Pt(NH_3)_2Cl_2]^{\circ}}$$

$$[Pt(NH_3)_4]^{++} \xrightarrow{Cl^-} [Pt(NH_3)_3Cl]^{+} \xrightarrow{Cl^-} \underset{\beta}{[Pt(NH_3)_2Cl_2]^{\circ}}$$

The intermediate compounds have been isolated and each step has been carried out separately.

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[2] Since the discovery of these compounds, considerable confusion has arisen in regard to their names. They were first known as the chlorides of Peyrone and of Reiset, respectively, and later as plato semi-diammine and platosammine chloride. In 1893 Werner introduced the terms α and β; finally, Drew and his collaborators, for no very good reason, reversed the usage of α and β. In this article Werner's nomenclature will be retained.

The problem of explaining the existence of the α- and β-compounds resolves itself, as a first step, into deciding whether they are (*a*) isomers (structural or geometrical), or (*b*) polymers, or (*c*) dimorphs. These alternatives, though not explicitly formulated by the earlier workers, can, as a result of their work, be narrowed down. The last was eliminated first. Cleve (22), a very active early worker in this field, clearly established the different chemical behavior of the α- and β-forms of $[Pt(NH_3)_2Cl_2]$. By treating each form with a series of reagents, including the appropriate silver salts, he prepared and described new (isomeric) compounds such as the α- and β-forms of $[Pt(NH_3)_2Br_2]$, $[Pt(NH_3)_2I_2]$, $[Pt(NH_3)_2(CN)_2]$, $[Pt(NH_3)_2(NO_3)_2]$, and $[Pt(NH_3)_2(NO_2)_2]$.

Although this and later work leaves no doubt that the α- and β-forms are not just simply different crystalline modifications of the same substance, it is interesting to note recent confirmation along physical lines. Dimorphous molecular crystals contain the same molecules packed in different ways, so that when each crystal structure is broken down by solution in any given solvent, the resulting solutions should be identical, a point which can, for example, be tested by an examination of absorption spectra (105). Small, but definite, differences have been noted in the absorption spectra of the aqueous solutions of the α- and β-forms of $[Pt(NH_3)_2Cl_2]$ (4). There is little doubt that, had chemical and physical tests along these lines been carefully applied, many of the issues created by the announcement of an alleged third (γ) form of $[Pt(NH_3)_2Cl_2]$ (43) would have been avoided.

If we make the assumption that the coördination number of Pt^{II} is four,[3] and experience has shown this to be practically universal, the number of polymers of the empirical composition $[Pt(NH_3)_2Cl_2]_x$ is, for $x > 1$, limited to the following:

1. $[Pt(NH_3)_4][PtCl_4]$ (88)
2. $[Pt(NH_3)_3Cl][Pt(NH_3)Cl_3]$ (122, 124)
3. $[Pt(NH_3)_4][Pt(NH_3)Cl_3]_2$ (23)
4. $[Pt(NH_3)_3Cl]_2^-[PtCl_4]$ (22)

The α- and β-diammines are distinct from all of these. Anticipating the discussion in a subsequent section, one may add that, with one rather puzzling exception, molecular-weight measurements on α- and β-forms of compounds of the type $[PtA_2X_2]$ (where $A = NH_3$, pyridine, $C_2H_5NH_2$, etc., and $X = Cl$, Br, CNS, OH, etc.) show that both forms are monomeric.

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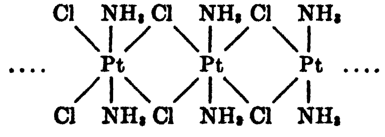
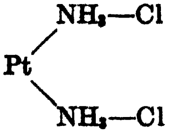
[3] Unless this limitation is specified it would be necessary to consider a structure like:

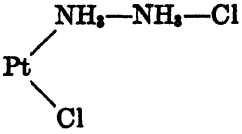


There is, however, no evidence for this structure among any platinous compounds of the empirical composition $Pt(NH_3)_2Cl_2$. Some extremely rare instances were Pt^{II} may possibly be octahedrally coördinated will be referred to later.

With the elimination of the possibilities (*b*) and (*c*)—polymerism and dimorphism, respectively—the problem now resolves itself into deciding whether the α- and β-diammines are structural or geometrical isomers. One of the first attempts to understand their constitution was made by Cleve (22), who proposed structures which, in the light of the then prevailing theories of valency, seemed plausible enough. They were:



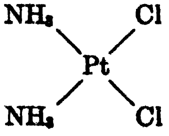
α



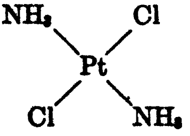
β

These formulations, which were also supported by Blomstrand, Jorgensen, and others, implied, of course, that the substances were structural isomers. With present-day knowledge of atomic structure, which enables an upper limit to be placed on the number of covalent bonds that can be formed by first-row elements of the Periodic Table, these structures can be ruled out immediately, since they both involve five covalent bonds to nitrogen. As will appear in the sequel, there are many other reasons for rejecting them. Nevertheless some attempt was made to revive them a few years ago (43) and they are occasionally still seriously discussed in the literature. The revival was the result of an attempt to explain certain reactions of the two compounds but, without going into detail, it can be stated that all these reactions can equally well be explained on an alternative view of their constitution.

While Cleve's formulations of the two compounds are no longer tenable, they served a very useful purpose in focusing attention on the problem of their constitution. Some fifteen years after Cleve's work, Jorgensen (77) set out to determine experimentally whether the assignment of the structures to the α- and β-forms as above had been correct, and in so doing he laid the experimental foundation upon which one of the most important advances in our knowledge of the structure of platinous compounds was made. This was Werner's introduction of the hypothesis of square coördination. Rejecting all previous explanations in terms of structural isomerism, Werner (152) applied to the problem the principles which he so successfully used to account for the constitution of the cobaltic ammines. Realizing that, unlike cobaltic ammines, which were universally characterized by a coördination number of six, the compounds of platinous platinum were always four coördinated, he put forward the idea that the α- and β-diammines were geometrical isomers (*cis* and *trans*), owing their existence to a planar distribution of the four bonds about the platinum atom, as shown below:



α(*cis*)



β(*trans*)

With regular tetrahedral bonds from platinum, two isomeric diammines are not possible. Although it would seem that Werner never at any time explicitly stated that the coplanar bonds were directed towards the corners of a square, it is clear from the diagrams of his classical 1893 paper that he considered them to be so directed. He never stressed the size of the bond angles in the plane, presumably because it was not essential in explaining the geometrical isomerism. Actually, the term "*square* coördination" was first used by Pauling (117) in connection with his quantum-mechanical treatment of the directed valence bond.

Strictly speaking, any one of a number of structures would equally well account for the geometrical isomerism of the α- and β-dichlorodiammines. The four bonds from platinum might be directed towards: (*a*) the corners of a tetragonal or rhombic bisphenoid (figure 1a shows the former); (*b*) and (*c*) the corners of a square (figure 1b) or a rectangle (figure 1c); (*d*) the corners of a tetragonal or rhombic pyramid (figure 1d shows the former). Each one of these alternatives has been introduced from time to time to explain the results of some chemical investigation. Thus, the structure shown in figure 1a was discussed by Rosenheim and Gerb (38) in explaining the existence of certain supposedly optically active platinous and palladous complexes. Drew and his collaborators (44) appear to have had the configurations shown in figures 1a and 1c in mind when formulating the hypothesis of paired coördination links to account for the structure of certain tetrammines. The pyramidal structure, figure 1d, was suggested by Dwyer and Mellor (45) as a means of reconciling results of certain experiments on mirror-image and geometrical isomerism.

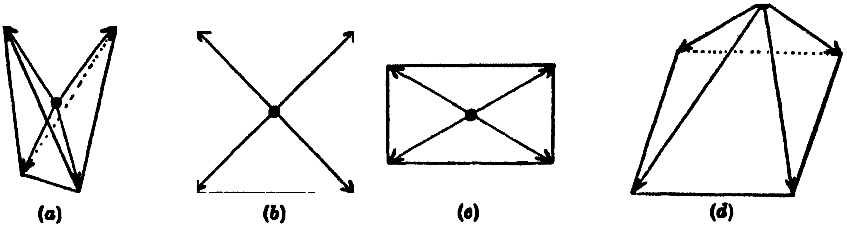


FIG. 1. Possible structures to account for the geometrical isomerism of the α- and β-forms of dichlorodiammineplatinum.

It does not seem to have been widely realized that the results of purely chemical methods of investigation (study of composition, isomerism, reactions, etc.) fail to provide a unique solution to the problem of the structure of platinous compounds and that herein lies the origin of much of the controversy in this field. To distinguish between the alternative structures (figure 1, a to d) it is necessary to have some information about the sizes of the angles between the four platinum bonds. Since the phenomena of geometrical and mirror-image isomerism depend primarily on molecular symmetry, they reveal nothing about the dimensions of bonds or the sizes of the angles between them. For optical activity to appear in the molecule $CR_1R_2R_3R_4$, all that is necessary is that the bonds have a general tetrahedral orientation; there is no need for the angle of the bond

R_1—C—R_2 to be 109°28′,—it might be 140° or more. Similarly, the existence of *cis* and *trans* isomerism among platinous compounds cannot be used to draw any inferences about the size of bond angles; any one of the above models might equally well be used to account for the geometrical isomerism. In view of the impasse which confronts the chemical method, it would perhaps be more logical to pass on to physical methods of studying the problem. This course will not be followed, partly for historical reasons and partly because, although the chemical evidence does not permit a single unequivocal choice, it does allow the alternatives to be narrowed down. This last can be achieved by combining the evidence from the study of geometrical and of mirror-image isomerism. To avoid unnecessary repetition of qualifying statements, the correctness of Werner's hypothesis will be assumed in the following sections dealing with geometrical isomerism.

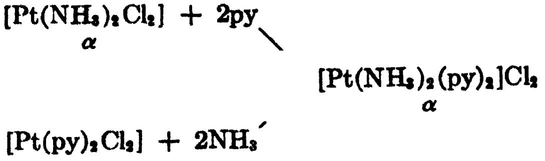
III. GEOMETRICAL ISOMERISM

A. THE DETERMINATION OF THE CONFIGURATION OF THE DIAMMINES

Having decided that the α- and β-diammines were geometrical isomers, Werner went a step further and by very ingenious reasoning determined which of the two forms was *cis* and which *trans*. The reactions concerned, first studied in detail by Jorgensen (77), may be summarized under two headings:

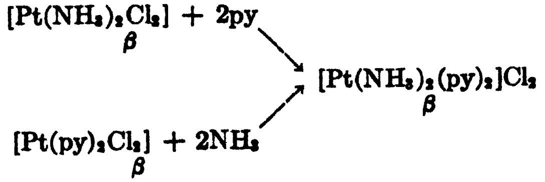
1. Addition reactions

When treated with two molecules of pyridine, α-dichlorodiammineplatinum forms α-diamminedipyridineplatinous chloride. This latter compound can also be prepared by treating α-dichlorodipyridineplatinum with two molecules of ammonia:



$$\begin{tikzcd}[column sep=small] \underset{\alpha}{[\mathrm{Pt(NH_3)_2Cl_2}]} + 2\mathrm{py} \arrow[dr] & \\ & \underset{\alpha}{[\mathrm{Pt(NH_3)_2(py)_2}]\mathrm{Cl_2}} \\ {[\mathrm{Pt(py)_2Cl_2}]} + 2\mathrm{NH_3} \arrow[ur] & \end{tikzcd} \qquad (1)$$

Similar reactions are observed with β-dichlorodiammineplatinum:



$$\begin{tikzcd}[column sep=small] \underset{\beta}{[\mathrm{Pt(NH_3)_2Cl_2}]} + 2\mathrm{py} \arrow[dr] & \\ & \underset{\beta}{[\mathrm{Pt(NH_3)_2(py)_2}]\mathrm{Cl_2}} \\ \underset{\beta}{[\mathrm{Pt(py)_2Cl_2}]} + 2\mathrm{NH_3} \arrow[ur] & \end{tikzcd} \qquad (2)$$

2. Elimination reactions[4]

When the solids are heated alone or aqueous solutions of them are warmed with concentrated hydrochloric acid, the α- and β-tetrammines revert to the dichlorodiammines. Thus α-dipyridinediammineplatinous chloride, when heated, reverts to β-dichloropyridinemonammineplatinum:

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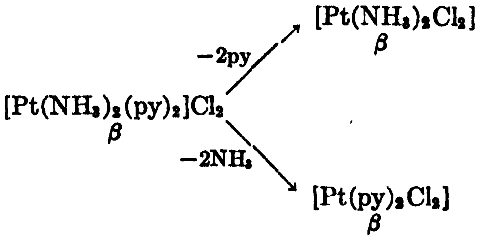
[4] These reactions might also be called substitution reactions if we regard them from the point of view of the complexion only. The names have been used in reference to the molecules as a whole.

$$\underset{\alpha}{[Pt(NH_3)_2(py)_2]Cl_2} \rightarrow \underset{\beta}{[Pt(NH_3)(py)Cl_2]} + NH_3 + py \qquad (3)$$

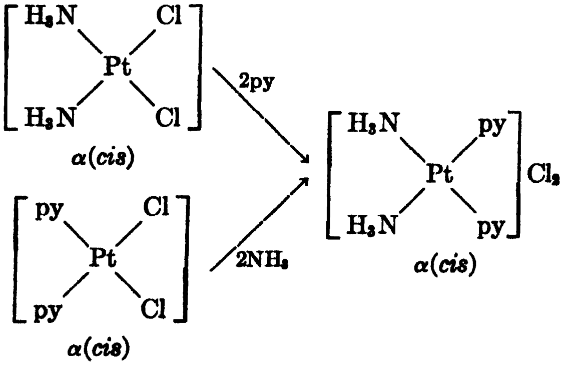
On the other hand, β-dipyridinediammineplatinous chloride gives rise to a mixture of β-dichlorodiammineplatinum and β-dichlorodipyridineplatinum:

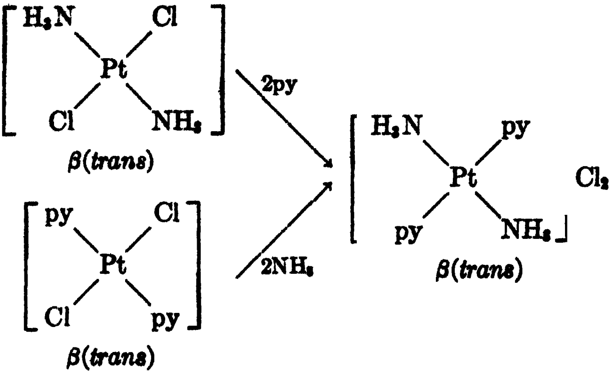


(4)

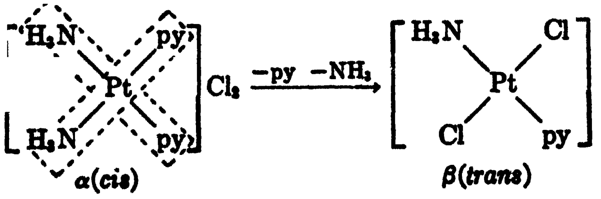
The last reaction has been queried by Reihlen and Nestle (131), but the experimental work of Jorgensen (77) and of Drew *et al.* (44) shows that the reaction which takes place is the one formulated. The products were separated by fractional crystallization and identified by preparing distinctive derivatives. All other addition and elimination reactions have been checked by Drew *et al.*, who used them, not to confirm Werner's hypothesis, but as a basis for the hypothesis of paired coördination links. Suffice it to say that the experimental foundation upon which Werner built his "configuration determination" has stood the test of time.

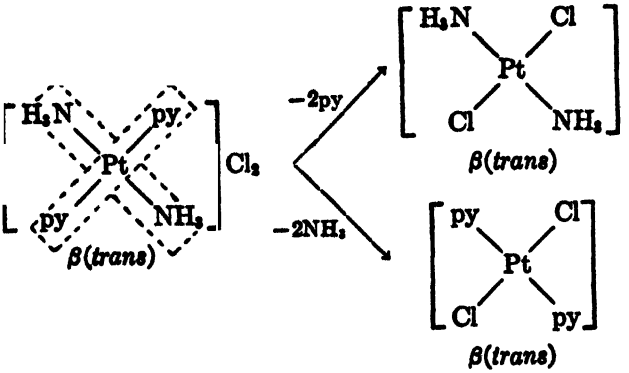
Whereas Jorgensen was forced to introduce several arbitrary assumptions to account for the above reactions in terms of structural isomerism, Werner was able to account for them in a perfectly straightforward manner with the help of only one further assumption, *viz.*, "*trans* elimination." Werner pictured reactions 1 to 4 as proceeding in the following manner:





In attributing the *cis* structure to the α-compound and the *trans* structure to the β-compound as above, Werner's final conclusions have been anticipated. His argument in support of this assignment is based on the assumption that, in the course of the elimination reactions, pairs of groups in *trans* positions only, are removed. The results of *trans* elimination are made clear in the following diagrams where the dotted lines enclose the eliminated *trans* pairs:





An examination of the structure of α(*cis*)-dipyridinediammineplatinous chloride will show that elimination of pairs of *cis* groups should result in the formation of a mixture of three compounds, *viz.*, $[Pt(NH_3)_2Cl_2]$, $[Pt(py)_2Cl_2]$, and $[Pt(py)(NH_3)Cl_2]$, whereas actually only one, the last, is obtained. On the other hand, *cis* elimination from the β(*trans*)-dipyridinediammine complex should result in the formation of only one compound, *viz.*, $[Pt(py)(NH_3)Cl_2]$; actually two are found, $[Pt(py)_2Cl_2]$, and $[Pt(NH_3)_2Cl_2]$. If we accept the hypothesis of *trans* elimination, all the reactions find consistent interpretation in terms of a *cis* structure for α-$[Pt(NH_3)_2Cl_2]$ and a *trans* structure for β-$[Pt(NH_3)_2Cl_2]$.

Such then is the experimental foundation upon which Werner, duly acknowledging his debt to Jorgensen, built the planar hypothesis. Yet nearly forty years later, protagonists of the view that the diammines were structural isomers charged Werner with "ignoring the relevant chemical evidence of his predecessors" when dealing with this problem (2).

Perhaps the only weakness in the interpretation of the elimination reactions is that at one stage (elimination from the α(*cis*)-$[Pt(py)_2(NH_3)_2Cl_2)]$ it depends on a negative result,—failure to find more than one compound. It is a striking tribute to Werner's remarkable insight into the structure of coördination compounds that all subsequent determinations of the configuration of α- and β-dichlorodiammineplatinum have proved the correctness of his assignment of *cis* and *trans* structures, and at the same time justified his hypothesis of *trans* elimination —at least for these reactions.

B. FURTHER CHEMICAL EVIDENCE CONFIRMING WERNER'S ALLOCATION OF CONFIGURATIONS

With the exception of results from dipole-moment studies and from one or two incomplete x-ray crystal analyses, confirmation of Werner's work on configuration has been obtained along chemical lines.

In the course of extensive investigations of "ammoniacal platinum bases," Cleve (22) reported a very interesting difference in the behavior of the α- and β-forms of $[Pt(NH_3)_2(NO_3)_2]$ towards oxalic acid solution: the α-form was converted to a compound with the empirical composition $[Pt(NH_3)_2C_2O_4]$; the β-form to a compound with the composition $[Pt(NH_3)_2(C_2O_4H)_2]$. Some sixty years later Grünberg (60) confirmed these observations and first suggested their interpretation. In doing so he made use of a method developed by Werner in his study of *cis–trans* configurations among the octahedral complexes of Co^{III}. Thus, Grünberg proceeded on the assumption that the $C_2O_4^{--}$ group acted as a bidentate chelate only when it replaced two NO_3 groups in *cis* positions; when it replaced NO_3 groups in *trans* positions, the oxalic acid molecule occupied one coördination position. It is clearly sterically impossible for the $C_2O_4^{--}$ group to span *trans* positions if square bonding is to be maintained.[5]

Since the oxalate group enters α-$[Pt(NH_3)_2(NO_3)_2]$ as a bidentate chelate, this form obviously has the *cis* configuration.

Now α-$[Pt(NH_3)_2(NO_3)_2]$ is prepared by treating the corresponding (α) chloro compound with silver nitrate, and if it be assumed that the substitution of NO_3 for Cl occurs without change of configuration, then α-$[Pt(NH_3)_2Cl_2]$ must also be a *cis*-form, in agreement with Werner's contention. That no change of configuration does occur is shown by the behavior of the oxalato compounds towards hydrochloric acid: the oxalato compound made from *cis*-$[Pt(NH_3)_2(NO_3)_2]$ regenerates *cis*-$[Pt(NH_3)_2Cl_2]$, while the second oxalato compound regenerates the *trans*-dichloro compound. These reactions may be represented schematically:

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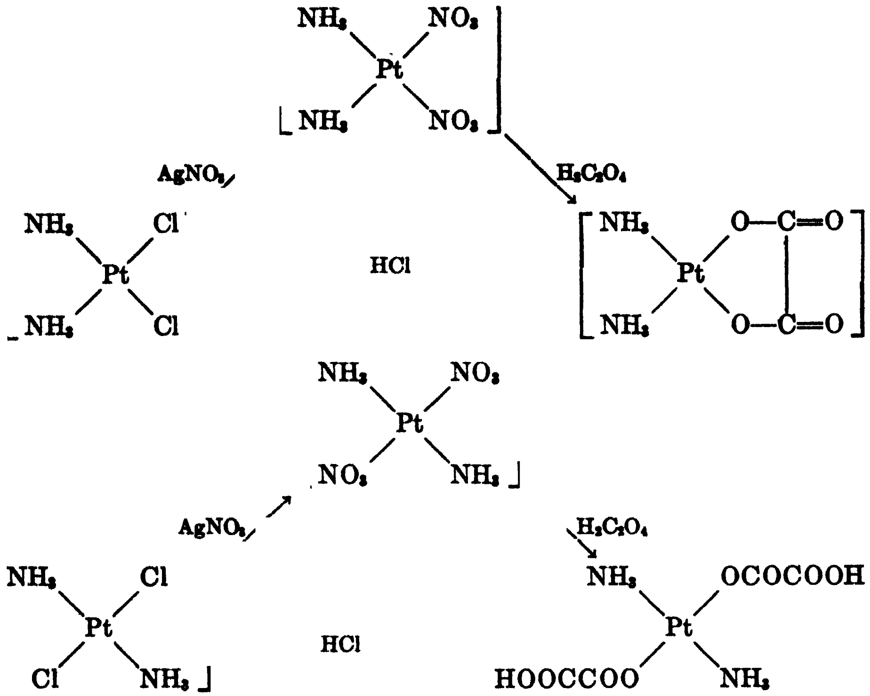
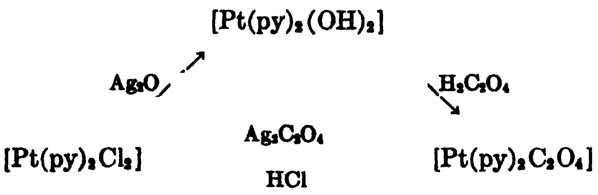
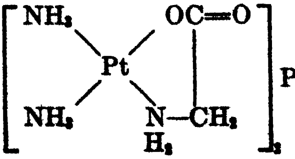
[5] The existence of the so-called *trans*-$Pt(py)_2SO_4$ would seem to be an exception to this statement. The compound is, however, a dihydrate and is probably $[Pt(py)_2(H_2O)_2]SO_4$.

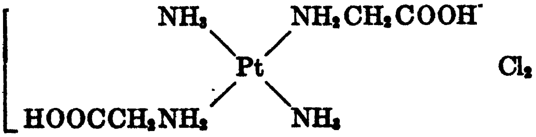


A very similar cycle of reactions has been carried out with α(*cis*)-$[Pt(py)_2Cl_2]$ (43).

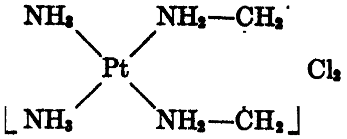


Cis(α)-$[Pt(py)_2Cl_2]$ also reacts with dipyridyl (dipy) to form $[Pt(py)_2dipy]Cl_2$ (114), whereas prolonged boiling of the *trans*(β)-form with alcoholic dipyridyl solution produces no detectable reaction (98). Passing reference only can be made to other work on the configuration of the dichlorodiammines; further confirmatory evidence is to be found in Grünberg and Ptizyn's (61) work on glycine complexes



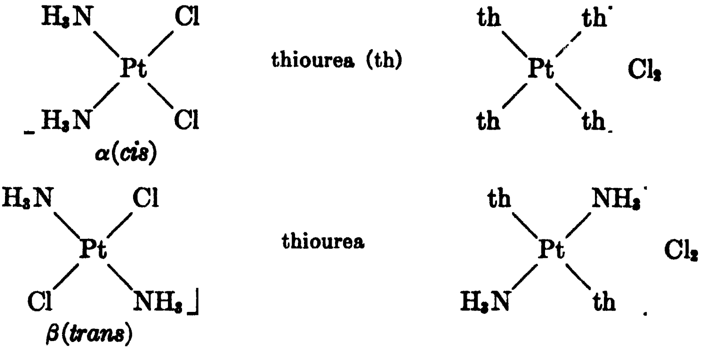


and also in some work by Drew (41), who has shown that α(*cis*)-$[Pt(NH_3)_2Cl_2]$ reacts with ethylenediamine to form $[Pt(NH_3)_2(NH_2CH_2CH_2NH_2)]Cl_2$,



whereas no reaction occurs with the *trans*-form.

Another method of discriminating between *cis*- and *trans*-$[PtA_2X_2]$ complexes depends on Kurnakow's (82) test, which is based on the reactions:



These reactions, in themselves, tell one nothing about structure in the sense that the ring-closure reactions do. Kurnakow's test has been very frequently used by Russian workers for deciding on the structure of platinous ammines. It would be interesting to know how widely applicable the test is, and it would be worth while to check it against other substances of known configuration, such as the thioether, stibine, arsine, and phosphine derivatives, described by Jensen (71, 73).

C. RELIABILITY OF THE CHEMICAL METHOD OF DETERMINING CONFIGURATION

A check on the reliability of the chemical method is afforded by dipole-moment measurements, which will be dealt with more fully in a subsequent section. Suffice it to say here that confirmatory evidence from this source has been obtained with *trans*-$[Pt(py)_2Cl_2]$ and with both forms of $[Pt((C_2H_5)_2S)_2Cl_2]$. The reactions of α-$[Pt((C_2H_5)_2S)_2Cl_2]$[6] reported by Angell *et al.* (2) show that it has a *cis* structure; the measured dipole moment of the compound bears this out. Dipole-moment measurements could not, unfortunately, be extended to the ammonia complexes, owing to their limited solubility in non-polar solvents.

One interesting point emerges from all this work and that is the remarkable stability of the configuration of platinous ammines, a circumstance which has greatly facilitated their study. There is no evidence that rearrangement of atoms or groups relative to one another occurs in a dichlorodiammine during

[6] This compound is referred to as the β-form by Angell and his collaborators.

chemical reaction, that is, a *trans*-compound retains its *trans* configuration through a series of reactions.[7] As Wells (150) has shown in his study of the structure of $Ag[Co(NH_3)_2(NO_2)_4]$, this constancy of configuration is not characteristic of all complexes. It is certainly not characteristic of square palladous complexes which, for some reason as yet unknown, are not as robust, in this sense, as those of platinous platinum.

D. MOLECULAR-WEIGHT DETERMINATIONS ON PtA_2X_2 COMPLEXES

Although all the possible polymeric forms of compounds with the empirical composition $Pt(NH_3)_2Cl_2$ have already been discussed, it is necessary to refer to this topic once again, because one of the first criticisms of the theory of square coördination originated in some work on molecular-weight determinations.

TABLE 1

Molecular weights and melting points of platinous compounds of the type $[PtA_2X_2]$

Jensen (71)

SUBSTANCE	MELTING POINT	MOLECULAR WEIGHT	
		Found	Calculated
	°C.		
trans-$[PtCl_2(Et_2Se)_2]$	60.0	549.0	540.7
cis-$[PtCl_2(Et_2Se)_2]$	74.0	618.0	540.7
trans-$[PtCl_2(Pr_2S)_2]$	80.0	531.0	502.5
cis-$[PtCl_2(Pr_2S)_2]$	85.0	598.0	502.5
trans-$[PtCl_2(Bu_2S)_2]$	60.0	564.0	558.4
cis-$[PtCl_2(Bu_2S)_2]$	84.5	612.0	558.4
trans-$(PtCl_2(i\text{-}Bu_2S)_2]$	110.0	538.0	558.4
cis-$[PtCl_2(i\text{-}Bu_2S)_2]$	138.5	672.0	558.4

Et = ethyl; Pr = propyl; Bu = butyl; *i*-Bu = isobutyl.

From a careful study of the vapor-pressure lowering in liquid ammonia solutions, Reihlen and Nestle (131) showed that *trans*-$[Pt(NH_3)_2Cl_2]$ was dimeric in that solvent. At the same time they showed that both forms (*cis* and *trans*) could be recovered unchanged from liquid ammonia and proved their technique by measurements on known substances. As the authors themselves point out, the dimerism of the *trans*-form does not prove the square hypothesis false. In spite of this and the fact that Fritzmann (53) had shown that both forms of $[Pt\{Se(C_5H_{11})_2\}_2Cl_2]$ were monomeric, Reihlen was so convinced that Werner's interpretation of the structures of the diammines was incorrect that he began a long series of experiments on optical activity, and eventually became one of the chief opponents of the theory of square coördination.

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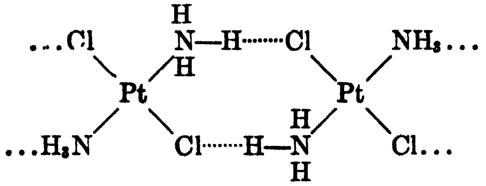
[7] This is, of course, not true of all platinous complexes; it has been reported, for example, that interconversion of *cis*- and *trans*-forms of various thioether complexes occurs quite readily (2).

An ebullioscopic determination of the molecular weight of *trans*-[$Pt(NH_3)_2Cl_2$] in aqueous solution, admittedly not very accurate (43), shows it to be monomeric in this solvent. King (80) has shown that the molecular weights of both forms of [$Pt(NH_3)_2(OH)_2$] are normal in aqueous solution. As far as other compounds of the type [PtA_2X_2] are concerned, there is plenty of evidence that both isomeric forms possess normal molecular weights. One may cite the work of Hantzsch (63) on α- and β-[$Pt(py)_2Cl_2$], of Grünberg (59) on α- and β-[$Pt(NH_3)_2(CNS)_2$], of Angell *et al.* (2) on α- and β-[$Pt((C_2H_5)_2S)_2Cl_2$], and finally the very extensive series of measurements by Jensen (71) on a wide range of thioether complexes (table 1). All this work leaves no doubt that the *cis*- and *trans*-compounds are monomeric in the solvents used. In Jensen's work there is some evidence of association of the *cis*-forms, but only to a small degree and in keeping with what one would expect from their higher dipole moment. It is interesting to note, too, the effect of the dipole moments on melting points; of the two, the *cis*-form melts at the higher temperature.

The problem of the dimerism of *trans*-[$Pt(NH_3)_2Cl_2$] in liquid ammonia still remains. If dipole moment were the principal factor determining association, one would expect the *cis*-form to be the one more associated. Any mechanism of association involving weak hydrogen bonds should operate with both isomers and might reasonably be expected to cause association beyond the dimer stage:



All that can be said at present is that the association of the *trans*-form in liquid ammonia is peculiar to this isomer and to this particular solvent, and, while inexplicable at the moment, it does not weaken the theory of square coördination. The importance of the work of Reihlen and Nestle lies not so much in the peculiarity of the results obtained as in the stimulus it gave to work on the optical activity of platinous compounds, to which we shall now turn.

IV. The Mirror-image Isomerism of Platinous Compounds

If two unsymmetrical chelate groups such as isobutylenediamine are tetrahedrally coördinated to a central metal atom, the resulting complex may exist in mirror image (figure 2a) but not *cis–trans* forms. On the other hand, if the chelate groups are coplanar, the complex may exist in *cis–trans*, but not mirror-image forms (figure 2b). Finally, if Pt^{II} forms pyramidal bonds, both geometrical (*cis–trans*) and mirror-image isomerism are possible; of the geometrical isomers, the *trans*-form only is capable of existing in mirror-image isomers. Over a number of years, Reihlen and his collaborators, working with various unsymmetrical chelate molecules (see figure 2a), have made repeated claims that they have obtained evidence proving the tetrahedral configuration of Pt^{II}.

Owing to the fact that these claims clash with the main body of evidence, it is necessary to examine them in some detail.

In the first place it must be pointed out that, except in one very doubtful instance, Reihlen and his collaborators have never followed the classical method of establishing a configuration by resolution through to its proper conclusion. That is to say, the allegedly optically active complexes have never been obtained free from the resolving acid (or base). In the one instance (132) where this separation was reported as having been carried out, the observed rotation was so very small (0.06° for a 4-dm. tube) as to be without any special significance. Reihlen's claims, then, rest on the observation that the molecular rotation, [*M*], of a salt like bis(aminomethyl-3-ethyl-4-methylquinoline)platinous α-bromocamphor-π-sulfonate (130) is greater (or less) than that calculated from the α-bromocamphor-π-sulfonate content of the salt. All attempts to obtain an optically active complex free from the acid used for resolution resulted in failure, which was attributed to racemisation. In view of the stability of platinous

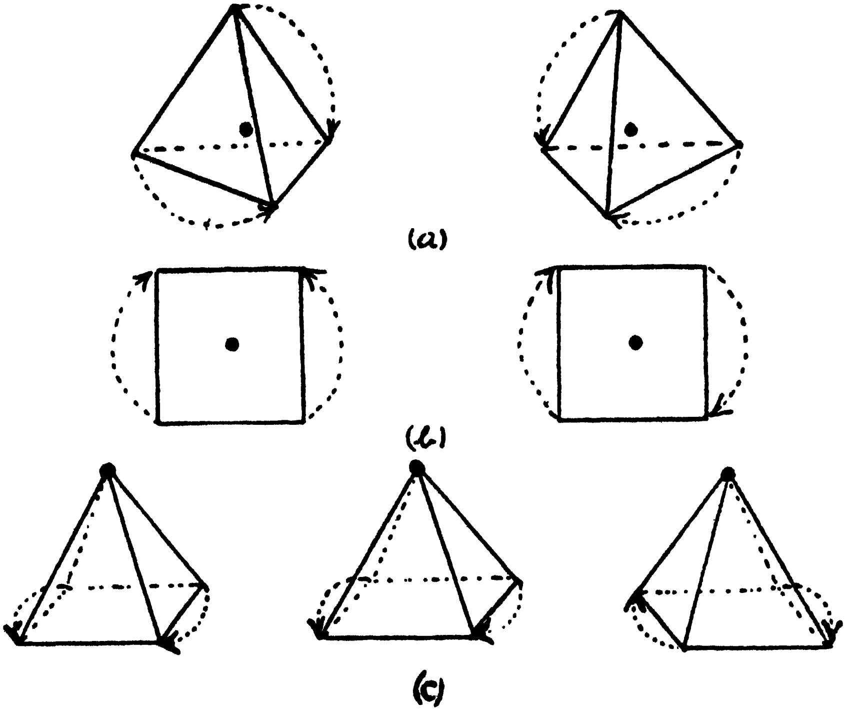
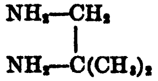


FIG. 2. Possibilities of isomerism when two unsymmetrical chelate groups are coördinated to a central metal atom. The arrow in these diagrams is used to indicate a molecule which by chelation produces an unsymmetrical ring, e.g.,

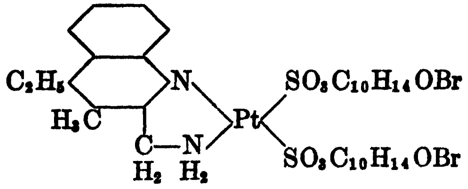


$$\begin{array}{l} NH_2\text{—}CH_2 \\ \qquad\;\; | \\ NH_2\text{—}C(CH_3)_2 \end{array}$$

complexes, already noted in an earlier section, this explanation is not specially convincing.

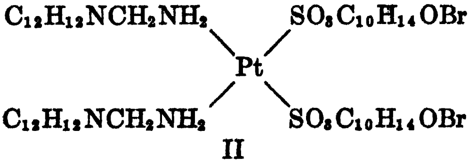
Unsuccessful attempts to obtain optically active platinous complexes have been reported by other workers. Ostromisslensky and Bergman (116) failed with $[PtClNH_3SO_3(py)]^-$, Tscherniaev (144) with $[Pt(NH_2OH)(NH_3)(py)(NO_2)]^+$, and finally Jensen (76) with bis(thiosemicarbazide)- and bis(2-aminomethyl-3-ethyl-4-methylquinoline)platinous ions. Significantly enough, in the last instance Jensen did note rotation differences of the same order as were observed by Reihlen and Huhn (130). However, on attempting to isolate an optically active platinous complex by precipitation with picric acid, Jensen found that the chloroform solution of the resulting picrate was always entirely devoid of optical activity. It is worth noting that several of the compounds upon which attempts at resolution were made have been described in the isomeric forms to be expected from square bonding: thus, two forms of bis(isobutylenediamine)platinous chloroplatinite (42) and bis(phenylethylenediamine-2-aminomethyl-3-ethyl-4-methylquinoline)platinous chloride (132) and three forms of $[Pt(NH_2OH)(NH_3)(py)(NO_2)]^+$ (143, 144) have been isolated. In the belief that Reihlen's resolutions were valid, Dwyer and Mellor (45) suggested a pyramidal structure for the complexes of platinum and palladium with a view to reconciling the findings on optical activity with the known *cis–trans* isomerism. This view is, of course, no longer tenable.

There still remains the question as to what causes the changes in rotation discovered by Reihlen and Jensen. The latter has made the suggestion that the bromocamphorsulfonate molecule becomes attached to the platinum atom itself, either (*1*) by forming the complex I



I

or (*2*) by opening the chelate rings to form II:

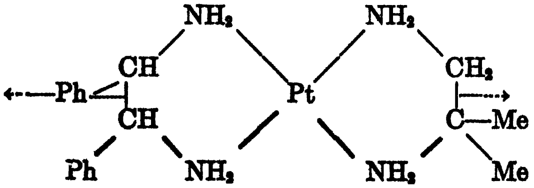


II

Jensen has calculated that contamination of bis(2-aminomethyl-3-ethyl-4-methylquinoline)platinous α-bromocamphor-π-sulfonate with as much as 5 per cent of I makes so very little difference in the analytical figures that it would not be detected. Formation of substance II would not alter the analytical results. Experiment shows (76) that on the addition of hydrochloric acid to bis(2-aminomethyl-3-ethyl-4-methylquinoline)platinous α-bromocamphor-π-sulfonate (which may be contaminated with I or II, or both), the molecular rotation returns to its normal value, i.e., the value for the free bromocamphorsulfonic acid. Jensen explains this behavior as being due to the freeing of the bromocamphorsulfonic acid from I and/or II. Whether we accept Jensen's explanation of the rotation changes or not, the fact remains that none of the foregoing optical evidence can be said to favor the view that Pt^{II} is tetrahedrally coördinated. Rather does it constitute negative evidence for alternative structures, but such evidence is seldom very convincing because we cannot be certain that the cause or causes of the negative result are exactly what we imagine them to be.

The unsatisfactory situation of the resolution work just described has been largely cleared up by Mills and Quibell (111), who were the first to describe stable optically active derivatives of Pt^{II}. Unfortunately, as far as the unequivocal proof of the square structure goes, the work of Mills and Quibell on mirror-image isomerism leaves us in much the same position as does the work on geometrical isomerism; that is to say, their results are quite consistent with the square structure, but they may be explained in terms of other configurations.

As they were doubtful of the interpretation of the work[8] on geometrical isomerism, Mills and Quibell planned and achieved the synthesis of a very ingeniously devised complex which, if planar, would have the symmetry properties required to produce mirror-image isomers. As represented below



the molecule possesses neither a plane nor a center of symmetry and is therefore resolvable. On the other hand, if the chelate group on the left (meso-stilbenediamine) were fixed, while the chelate group on the right were rotated through 90°, so bringing about a tetrahedral distribution of the four bonds to platinum, the molecule as a whole would possess a plane of symmetry. In other words, the molecule with a tetrahedral configuration would no longer be resolvable.

In point of fact, Mills and Quibell were able to isolate, quite free from the resolving acid (*d*-diacetyltartaric), optically active salts whose great stability is entirely in keeping with what is known of the robustness of platinous complexes. And so for the first time the method of resolution was used to provide evidence for the square configuration. In the light of the general body of evidence, more especially the physical, there is no doubt that these optically active complexes are square, but as Mills and Quibell themselves point out, the results might also have been attributed to a pyramidal arrangement. However, they regarded this last configuration as inherently improbable, pointing out that if it were the explanation of their results, then certain simpler complexes should be resolvable. Inherent improbability is not necessarily a safe argument, as the recent discovery of the pyramidal arrangement of four covalent bonds about Pb^{II} (113) will serve to show.

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[8] "Although the frequency with which isomerism occurs in compounds containing a complex of the type A_2PtB_2 gives great weight to Werner's interpretation, yet it is always difficult in dealing with geometrical isomerism to make certain that the isomerism is actually of the nature supposed. There is no such difficulty with mirror image isomerism" (111).

Summing up the chemical evidence, one may say that it definitely rules out the regular tetrahedral and tetragonal bisphenoidal arrangements, is consistent with the theory of square coördination, but leaves the possibility of pyramidal and rectangular arrangements in doubt. For the final stages of the proof of structure we must turn to physical methods.

V. RAMAN AND INFRARED SPECTRA

In applying Raman and infrared spectra to unravelling problems of molecular structure the procedure is, briefly, as follows: Various molecular models are set up and the modes of vibration of each are systematically examined. According as the modes of vibration produce changes in the degree of polarizability or dipole moment of the molecule, the corresponding vibration frequencies will be responsible for lines in the Raman and infrared spectrum, respectively. The number of lines in each spectrum and the state of polarization of the Raman lines are deduced for each model and the model adopted is the one which gives exact or closest correspondence with the observed spectra. The number of Raman lines alone is not always a certain guide in deciding between alternative structures because there is always the risk that a line, though permitted, may be so faint as to escape detection. In the general case, if reliance is to be placed on structural conclusions, observations must be made on the polarization of the Raman lines and also on the absorption spectrum in the infrared region.

TABLE 2

Raman and infrared spectra of molecules of the type $A(XY)_4$

MODEL	SYMMETRY	RAMAN FREQUENCIES	INFRARED FREQUENCIES	INACTIVE FREQUENCIES	COINCIDENCES
Square	D_{4h}	7 (2)*	6	3	0
Tetrahedral	T_d	8 (2)	4	1	4
Pyramidal (square base)	C_{4v}	15 (4)	9	1	9
Rectangular	D_{2h}	9 (4)	12	2	0
Pyramidal (rectangular base)	C_{2v}	21 (6)	16	0	16

* The figures in parentheses refer to the number of polarized lines.

As far as square complexes are concerned, the simplest spectra are to be expected from an ion like $[PtCl_4]^{--}$ but, owing to difficulties associated with observing the Raman spectra of highly colored solutions, $K_2[PtCl_4]$ has not been investigated. Mathieu (96), who has been mainly responsible for work in this field, has studied the following colorless or nearly colorless compounds:

$Na_2[Pt(CN)_4]$, $Na_2[Pt(NO_2)_4]$, $[Pt(NH_3)_4]Cl_2$, $[Pt(py)_4]Cl_2$, and $[Pt(en)_2]Cl_2$; of these, only the first provided sufficient information for any structural conclusions to be drawn. Observations were made on the number and polarization of the Raman lines and were discussed primarily from the standpoint of square and tetrahedral models. The observed Raman spectrum of $Na_2[Pt(CN)_4]$ comprised six lines, two of which were polarized; these data favor the square structure but do not constitute decisive evidence for it. The position can best be understood by reference to table 2[9], which shows the frequencies to be expected for different models of a molecule of the type $A(XY)_4$ with the atoms AXY collinear. It will be seen at once that the experimental data rule out the last three less symmetrical configurations. A clear-cut distinction between the first two models, in favor of the square structure, is most likely to be obtained by extending observations to the infrared, where the observation of five or more fundamental frequencies would definitely exclude the tetrahedral model. As the position stands, the evidence for the square structure is essentially negative in character; the number of Raman lines does not exceed that predicted for the square model. It is of course always more satisfying to have positive evidence on a point like this and there is a good case for extending work to the infrared.

VI. EVIDENCE FROM DIPOLE MOMENTS

Whereas all diatomic molecules of the type A—A are electrically symmetrical and non-polar, those of the type A—B always have a permanent electric moment. In a polyatomic molecule, each bond A—B is associated with a dipole moment which can be treated as a vector quantity, the permanent dipole moment of the molecule as a whole being the vector sum of the individual bond moments. For any molecule with a center of symmetry, the vector sum of the bond dipole moments will be zero, that is, the molecule will have no permanent dipole moment. This is found to be true of a number of molecules whose structures have been ascertained by other means; thus CO_2, SF_6, and *trans*-dichloroethylene are all centrosymmetrical and without permanent dipole moment. In using dipole moments as a test for the presence of a center of symmetry it must be remembered that the converse of the above proposition is not necessarily true, that is to say, there are molecules like CCl_4, with zero dipole moment, which do not have a center of symmetry. However, of the configurations listed on page 153 only two have a center of symmetry; for all the others the vector sum of the dipoles will not, in general, be zero.

Among the dipole studies of metal complexes, those of Jensen (71, 73), dealing with isomerides of the type $[PtA_2X_2]$, have an important bearing on the present discussion. The results of some of Jensen's measurements are set out in table 3, from which it can be seen that the compounds fall into two groups. In the first, where A is represented by various symmetrically substituted arsines, phosphines, and stibines, and X by NO_2, Cl, Br, etc., the moments are either approximately zero or around 8–12 Debye units. The compounds with zero moment are obviously the *trans*-forms and those with the large moment, the *cis*-forms. In $\mathrm{PtCl_2((CH_3)_3As)_2}$, for example, the resultant of the three As—C bond moments is directed along the Pt—As bond irrespective of whether there is, or is not,

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[9] I am indebted to Mr. A. Maccoll for the compilation of this table.

TABLE 3

Dipole moments of platinous compounds of the type $\mathrm{PtA_2X_2}$

Jensen (71, 73)

COMPOUND	DIPOLE MOMENT	COMPOUND	DIPOLE MOMENT
	Debye units		*Debye units*
trans-$[\mathrm{PtBr_2(Et_3P)_2}]$	0	*cis*-$[\mathrm{PtBr_2(Et_3P)_2}]$	11.2
trans-$[\mathrm{PtI_2(Et_3P)_2}]$	0	*cis*-$[\mathrm{PtI_2(Et_3P)_2}]$	8.2
trans-$[\mathrm{PtCl_2(Pr_3P)_2}]$	0	*cis*-$\mathrm{PtCl_2(Pr_3P)_2}$	11.5
trans-$[\mathrm{PtCl_2(Et_3As)_2}]$	0	*cis*-$[\mathrm{PtCl_2(Et_3As)_2}]$	10.5
trans-$[\mathrm{PtI_2(Et_3Sb)_2}]$	0	*cis*-$[\mathrm{PtCl_2(Et_3Sb)_2}]$	9.2
trans-$[\mathrm{PtCl_2(Bu_3P)_2}]$	0	*cis*-$[\mathrm{PtCl_2(Bu_3P)_2}]$	11.5
trans-$[\mathrm{PtCl_2(Pr_2S)_2}]$	2.35	*cis*-$[\mathrm{PtCl_2(Pr_2S)_2}]$	9.5
trans-$[\mathrm{PtCl_2(Bu_2S)_2}]$	2.35	*cis*-$[\mathrm{PtCl_2(Bu_2S)_2}]$	9.2
trans-$[\mathrm{Pt(NO_2)_2(Pr_2S)_2}]$	2.48	*cis*-$[\mathrm{Pt(NO_2)_2(Pr_2S)_2}]$	13.1
trans-$[\mathrm{PtBr_2(Et_2S)_2}]$	2.26	*cis*-$[\mathrm{PtBr_2(Et_2S)_2}]$	8.9

Et = ethyl; Pr = propyl; Bu = butyl.

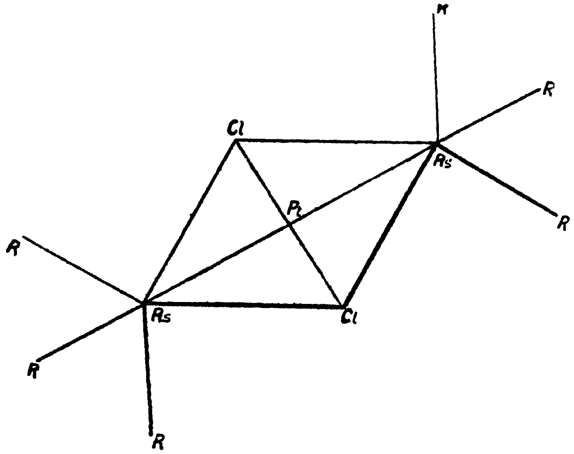


FIG. 3. *Trans*-planar structure for $[\mathrm{PtCl_2((CH_3)_3As)_2}]$

rotation about the Pt—As bond. The only reasonable structure for $[\mathrm{PtCl_2((CH_3)_3As)_2}]$ which could give zero moment is the *trans*-planar (figure 3).

In the second group, which comprises the thioether complexes, there is a large difference between the α- and β-forms, the dipole of neither form being zero. However, it is concluded that the compounds with the larger moments are the *cis*-forms and those with the smaller the *trans*-forms. If we make the reasonable assumption that in *trans*-[Pt($(C_2H_5)_2S)_2Cl_2$] the platinum bonds are coplanar, the small moment of the molecule can be accounted for in terms of the known configuration of tercovalent sulfur. Indeed, the moment of the *trans*-form may be looked upon as supplying further proof that the three sulfur valence bonds are not coplanar. Figure 4 will make it clear that the S—C moments are not directed along the direction of the Pt—S bond, and that the molecule as a whole must have a resultant dipole moment,—in other words, the molecule in figure 4 has a *trans–cis* structure.

Jensen's work provides a neat physical method for determining the configuration of metal complexes and at the same time confirms the results of chemical methods of attack on this problem. More important still, it shows that the complexes are strictly planar, and in fact constitutes one of the strongest pieces of evidence against any suggestion of a pyramidal configuration. From the relevant dipole data it is estimated that the platinum atom cannot, at most, be more than 0.08 Å. from the plane of the four attached groups. Dipole measurements do not tell us what the magnitudes of the Cl—Pt—As bond angles are, and hence do not enable us to say whether the coördination is square

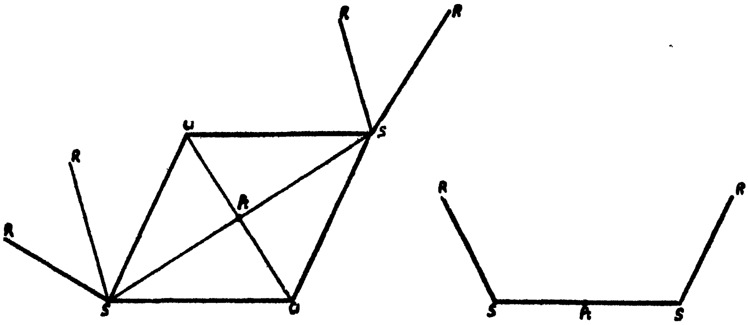
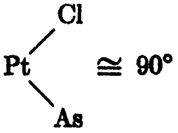


FIG. 4



$$\text{Pt}\begin{matrix}\diagup\text{Cl}\\ \diagdown\text{As}\end{matrix} \cong 90°$$

or not. Departures from angles of 90° do not disturb the centrosymmetry of the complex.

VII. THE CRYSTAL STRUCTURE OF PLATINOUS COMPOUNDS

When based on sufficient reliable intensity data and carried through to completion, x-ray crystal analysis may be looked upon as a final court of appeal in structural problems. Often, however, a crystal may be so complicated and the difficulties associated with its determination so great that only a partial solution can be obtained. Evidence from crystal-structure analyses must therefore be given varying weight according to the completeness of the analysis, always assuming of course that each stage has been reliably determined. Several stages in an analysis may be recognized: (*1*) The determination of the size of the unit cell and the number of molecules contained therein. As a rule the number of molecules per unit cell determines to a large extent the complexity of a structure. If there happen to be a large number of molecules, in themselves fairly complicated, the task may prove extremely difficult, if not impossible, at this stage of the development of x-ray technique. An investigation terminated at the first stage is of little use, although on several occasions attempts have been made to use the fact that one of the dimensions of a unit cell is very small, to prove the existence of some planar structure. Conclusions based on such slender evidence must be accepted with caution, because a small cell dimension may be explained in some other way.[10]

(*2*) The second stage leads to the determination of the space group which describes fully the symmetry of the crystal structure. Once the number of molecules per unit cell and the space group have been determined, it is possible to state the symmetry elements of the molecule itself. By these means the following molecules (or ions) have been shown to have a center of symmetry: (*a*) bis(salicylaldoxime)platinum (25); (*b*) bis(dimethylsulfine)dichloroplatinum (27); (*c*) bis(ethylenediamine)platinous ion (26). In all these instances centrosymmetry is consistent with *trans*-planar structures for the complexes, but not with tetrahedral structures.

(*3*) The third and final step involves finding the exact location of each atom in the unit cell, and as a rule this becomes increasingly difficult as the number of parameters required to fix these positions increases. Relatively few complete structure determinations have been made on platinous compounds and they have, for the most part, been confined to fairly simple structures. Nevertheless the results are of great stereochemical interest. The structures of the following substances have been completely determined and in every instance square complexes have been found:

(1) $K_2[PtCl_4]$ (figure 5)

(2) $[Pt(NH_3)_4]Cl_2H_2O$ (figure 6)

(3) $K_2[Pt(C_2O_2S_2)_2]$ (figure 7)

(4) $PtC_{32}H_{16}N_8$

(5) PtS (figure 8)

The first substance examined was $K_2[PtCl_4]$ (38), which along with K_2PdCl_4 belongs to the tetragonal system and has one molecule per unit cell. Because $K_2[PtCl_4]$ and $[Pt(NH_3)_4]Cl_2$ form the starting materials for the preparation of many of the isomeric ammines discussed earlier and in this sense are key substances, their structure will be discussed in detail. K_2PtCl_4 possesses an unusually simple structure, involving as it does but one parameter, a parameter to fix the position of the chlorine atom in the plane of the platinum atoms, as shown in figure 5. The positions of the potassium and platinum atoms are fixed uniquely by symmetry. In the absence of any crystal faces indicating the contrary, Dickinson assumed that the crystal belonged to the holohedral class and his final structure determination in a sense justified this assumption. Nevertheless it is always useful to have some independent evidence of the absence of lower symmetry in the crystal. Such has been provided by piezoelectric tests (142) and pyroelectric tests (106), both of which show that the crystal does not lack a center of symmetry.

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[10] Because one of its cell dimensions is small as compared with others, it has been suggested (31) that the compound $Co(py)_2Cl_2$ contains square-coördinated Co^{II}. Magnetic evidence is against this suggestion, and the small cell dimension can be explained on the basis of an octahedral structure (101).

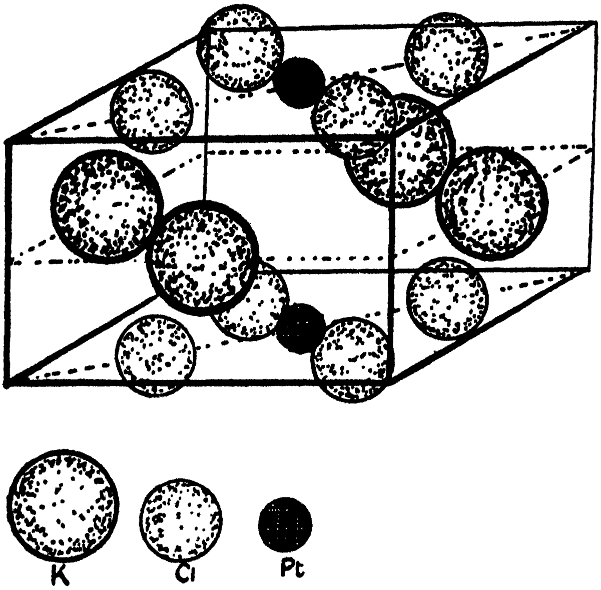

FIG. 5. The structure of $K_2[PtCl_4]$

The isomorphous palladium compound has been reinvestigated with more recently developed x-ray technique by Theilacker (142), and Dickinson's (38) earlier work has been completely confirmed. From his intensity data Theilacker concludes that the palladium atom cannot, at most, be more than 0.2 Å. out of the plane of the four chlorine atoms, and that since this is not much greater than the experimental error it is practically certain that all five atoms are strictly coplanar. If one accepts this evidence for the planar structure of the complex, then it follows immediately from the tetragonal symmetry of the crystal that the four Pt—Cl bonds are at exactly 90°, and that the $PtCl_4^{--}$ complex is definitely square. The stereochemical implications of this crystal structure determination were not at first fully realized. They are, however, most important, because for the first time accurate information of the orientation of the four platinum bonds became available. One or two additional points about the structure are worth noting. Firstly, the strong negative double refraction of the crystal (106) is consistent with the structure attributed to it. Several small discrepancies between observed and calculated intensities in Dickinson's work on K_2PtCl_4 can be explained on the basis of the anisotropic thermal motions of the platinum atoms (66). However, the thermal oscillations of platinum atoms are about fixed mean positions so that no modification of the square structure is required.

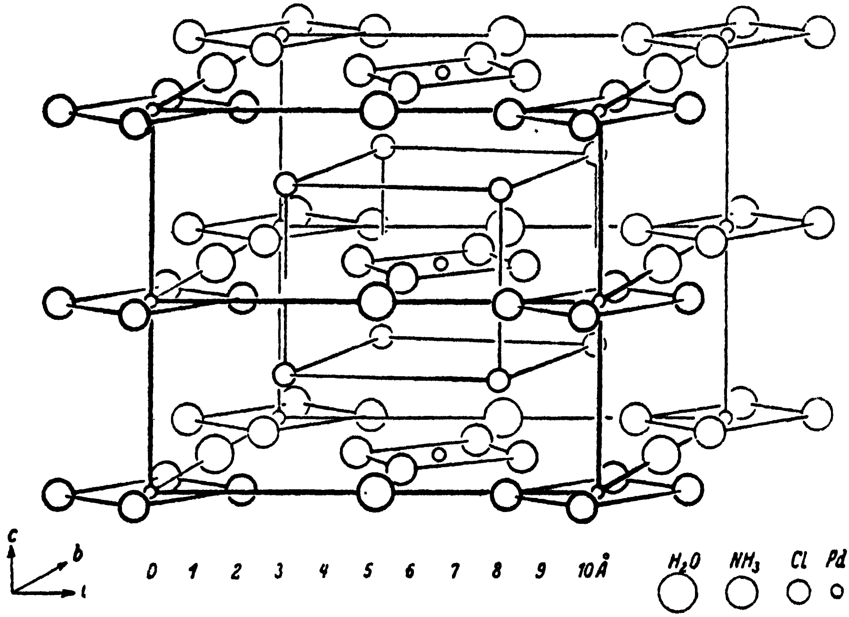

FIG. 6. The structure of $[Pd(NH_3)_4]Cl_2H_2O$ and of $[Pt(NH_3)_4]Cl_2H_2O$ (*Strukturbericht*)

The second relatively simple compound, $[Pt(NH_3)_4]Cl_2H_2O$, was first investigated by Cox (24), who assigned to it a structure the same in essentials as that of K_2PtCl_4,—with the two chloride ions occupying the positions of the two potassium ions and the $[Pt(NH_3)_4]^{++}$ that of $[PtCl_4]^{--}$. Subsequent work has shown that while the essential features of the $[Pt(NH_3)_4]^{++}$ complex are as Cox reported them (the four platinum valences coplanar and directed towards the corners of a square), the structure of the crystal is a little more complicated, requiring for its proper description a two-molecule unit cell (37).[11] The two-molecule cell arises from the small rotations of the $[Pt(NH_3)_4]^{++}$ complexes and chlorine atoms about the *c*-axis (figure 6). Robertson and Woodward's (136) analysis of platinous phthalocyanine is one of the most extraordinary x-ray analyses carried out to date, but it adds little to the general theme developed here. The phthalocyanine molecule is a huge planar molecule and any metal atom attaching itself to it by the four pyrrole nitrogen atoms must do so by coplanar bonds.

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[11] Dickinson's most detailed work actually related to the isomorphous palladous compound $Pd(NH_3)_4Cl_2 \cdot H_2O$.

In the crystals so far mentioned, the complexes have all belonged to the finite class. In the last crystal of the group, *viz.*, PtS (16), we find a new type,—an infinite complex extending throughout the crystal in three dimensions. Platinum and sulfur maintain a coördination number four by appropriate *sharing* of atoms; a portion of an infinite chain structure can be seen in the unit cell of PtS shown in figure 8.

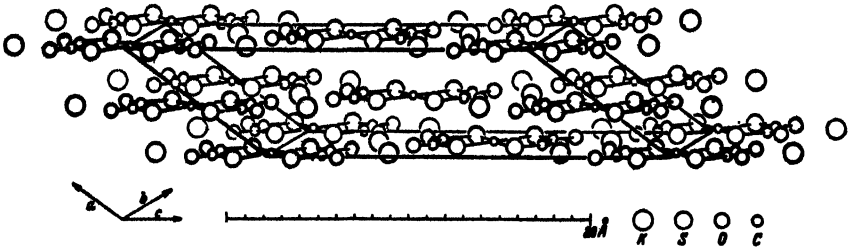


FIG. 7. The structure of $K_2[Pt(C_2O_2S_2)_2]$ (*Strukturbericht*)

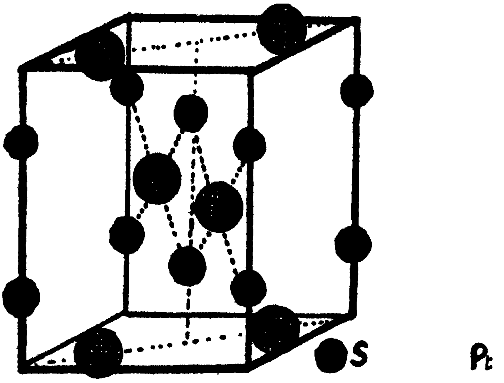


FIG. 8. The structure of PtS

Finally we come to several structures which have not been directly determined but which may be inferred from the complete crystal analysis of an isomorphous crystal. Square-coördinated metal complexes are found in each, and it must suffice merely to list them with the completely analyzed crystal indicated in brackets:

(a)	$Ba[Pt(CN)_4]4H_2O$	$\{(Ba[Ni(CN)_4]4H_2O)\}$	(13)
(b)	$Na_2[Pt(CN)_4]3H_2O$	$\{(Na_2[Ni(CN)_4]3H_2O)\}$	(15)
(c)	$PtCl_2$	$\{PdCl_2\}$	(15)
(d)	PtO	{PdO}	(113)

VIII. SOME OPTICAL PROPERTIES OF THE CRYSTALS OF PLATINOUS COMPOUNDS

Taken by itself, evidence from crystal optics is not specially significant, but in conjunction with other data it may often afford valuable confirmation of the existence of certain structural features in a crystal. It is interesting to recall that von Laue's discovery of the diffraction of x-rays, upon which the science of crystal analysis was built, was in no small measure conditioned by Ewald's theoretical studies of the double refraction to be expected from certain postulated atomic arrangements in crystals. The science of crystal analysis has amply repaid this debt by providing such a wealth of information about atomic arrangements as to enable the formulation of useful correlations between structure and optical properties.

TABLE 4

The birefringence of some platinous compounds

SUBSTANCE	SYMMETRY				DOUBLE REFRACTION	REFERENCES
$K_2[PtCl_4]$	Tetragonal	1.683		1.553	−0.130	(106)
$Ba[Pt(CN)_4]4H_2O$	Monoclinic	1.6706	1.677	1.8982	+0.2276	(153)
$Mg[Pt(CN)_4]7H_2O$	Tetragonal	1.561		1.910	+0.350	(55)
$LiK[Pt(CN)_4]3H_2O$	Orthorhombic	1.6237	1.6278	2.2916	+0.6679	(153)
trans-$[Pt(py)NH_3Cl_2]$	Triclinic	1.653	1.732	>1.79	>−0.137	(56)
cis-$[Pt(py)NH_3Cl_2]$	?	1.624	1.732	>1.79	>−0.166	(56)
$K[PtCl_3C_2H_4]H_2O$	Monoclinic	<1.627		1.717	>−0.090	(78)
$NH_4[PtCl_3C_2H_4]H_2O$	Monoclinic	<1.623		1.702	>?0.079	(78)
$Na_2[Pt(CN_4]3H_2O$	Triclinic				High and negative	(15)
$Sr[Pt(CN)_4]5H_2O$	Monoclinic	1.547	1.613	1.637	−0.090	(12)
$K_2[Pt(COS)_4]$	Monoclinic				Extremely high	(32)
$[Pt(NH_3)_2(NO_2)_2]$	?	1.531	1.779	(1.80)	−0.269	(155)
$[PtNH_3(py)Cl_2]$	?	1.653	1.732	1.79	−0.135	(155)
$[PtNH_3(py)(NO_2)_2]$	?	1.624	1.696	1.750	−0.126	(155)

The striking double refraction of crystals of the isomorphous series $CaCO_3$, $NaNO_3$, and $ScBO_3$, for which the presence of parallel planar XO_3 ions is responsible (10), suggested that similar optical properties would be found among crystals containing square-coördinated Pt^{II}.

According to the results of x-ray analysis the square $[PtCl_4]^{--}$ groups in K_2PtCl_4 are all arranged parallel to 001. If this arrangement is correct, the crystal should show strong negative double refraction, which indeed it does (106). Had the four chlorine atoms been tetrahedrally arranged about the platinum, one would have anticipated a small double refraction of the same order as that found in crystals containing SO_4^{--}, PO_4^{---}, ClO_4^-, etc.

Information about the crystal optics of other platinous compounds is summarized in table 4, from which it can be seen that the double refraction is high throughout. The high double refraction of Zeise's salt, K[PtC$_2$H$_4$Cl$_3$], is interesting; it is not known just how the ethylene is incorporated in the complex, but the complex undoubtedly has a square configuration.

The strength of the double refraction of a crystal will depend on mutual arrangement of any anisotropic units it may contain, being greatest, and negative, when they are all parallel to one another as in CaCO$_3$ and K$_2$PtCl$_4$. Certain arrangements of planar groups result in positive double refraction, as in bastnaesite (154); with other arrangements, less probable no doubt, it is conceivable that a very low double refraction could be produced. Thus, while high double refraction undoubtedly indicates the presence of highly anisotropic units in a structure, low double refraction does not necessarily mean that such units are absent. In this connection another situation which may arise must be kept in mind. Double refraction is subject to dispersion,—that is, it varies with wave length,—and one may just happen to choose, for making a measurement, a wave length where the double refraction is low or at a minimum. This point is well brought out in Brasseur and Rassenfosse's recent (12, 15) extensive studies of the crystal optics of a whole series of complex cyanides of the types Ba[Me(CN)$_4$]4H$_2$O, Ca[Me(CN)$_4$]5H$_2$O, Sr[Me(CN)$_4$]4H$_2$O, and Na$_2$[Me(CN)$_4$]-3H$_2$O, where Me = Pt, Pd, and Ni. Without exception, these substances show high double refraction, and for all except three, Ba[Pt(CN)$_4$]4H$_2$O, Mg[Pt(CN)$_4$]-7H$_2$O, and Ca[Pt(CN)$_4$]5H$_2$O, the sign of the double refraction is negative. A complete crystal-structure analysis of Ba[Ni(CN)$_4$]4H$_2$O reveals a structure which accords with high negative double refraction. The positive sign of the isomorphous platinum compound is an extremely puzzling anomaly for which no explanation has yet been given. There is little doubt about the observations on the positive sign, since the same results have been reported by several workers. It would seem that Bragg's theory of the origin of double refraction of planar complexes needs further refinement if it is to take account of these platinum compounds.

MAGNETIC ANISOTROPY

Practically nothing has been done on the diamagnetic properties of platinous compounds, but it can reasonably be expected that, like CaCO$_3$, NaNO$_3$, etc., they will show pronounced anisotropy. Some very early observations on Ca[Pt(CN)$_4$]5H$_2$O were made by Grailich (58), who reported that the direction of greatest diamagnetic susceptibility is parallel to the *c*-axis of the (orthorhombic) crystal. This would place the plane of the [Pt(CN)$_4$]$^{--}$ group approximately perpendicular to the *c*-axis, whereas the optical properties suggest a different orientation. The crystal optics of the isomorphous nickel compound, Ba[Ni(CN)$_4$]4H$_2$O, place the plane of the [Ni(CN)$_4$]$^{--}$ group approximately parallel to the *c*-axis, in qualitative agreement with the observations on the diamagnetic anisotropy of the platinum compound. Further work, possibly along the lines of that of Born (9) and Hylleraas (68) on quartz and calomel, is needed to clear up the anomalous behavior of these platinum compounds.

IX. DIRECTIVE INFLUENCES IN THE REACTIONS OF SQUARE COMPLEXES

A. *Trans* ELIMINATION

In the light of the crystal-structure determinations of $K_2[PtCl_4]$ and $[Pt(NH_3)_4]Cl_2H_2O$ it is of interest to note at this stage certain features of the reactions involved in the formation of the isomeric diammines. The most important of these is the process of *trans* elimination discovered by Werner. So far, little has been done towards providing a satisfactory understanding of this phenomenon, and all that will be attempted here will be to formulate some of the problems that arise. At the outset it is obvious that *trans* elimination cannot be a perfectly general reaction, because although it provides an explanation of some of the transformations, *cis* elimination must be invoked to explain others.

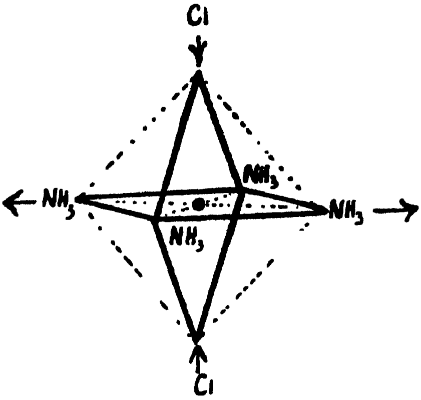


FIG. 9

Let us consider first the reaction responsible for the discovery of *trans* elimination:

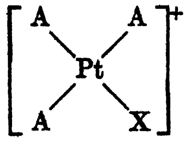
$$[Pt(NH_3)_4]^{++} \xrightarrow{2HCl} \underset{trans}{[Pt(NH_3)_2Cl_2]}$$

If we regard the elimination of the two molecules of ammonia as occurring simultaneously, we might suppose that as the two *trans* molecules depart, two chlorine atoms enter the *trans* octahedral positions to form a new *trans* square complex, as shown in figure 9. But matters are not so simple as this. As already pointed out, the two reactions below proceed stepwise:

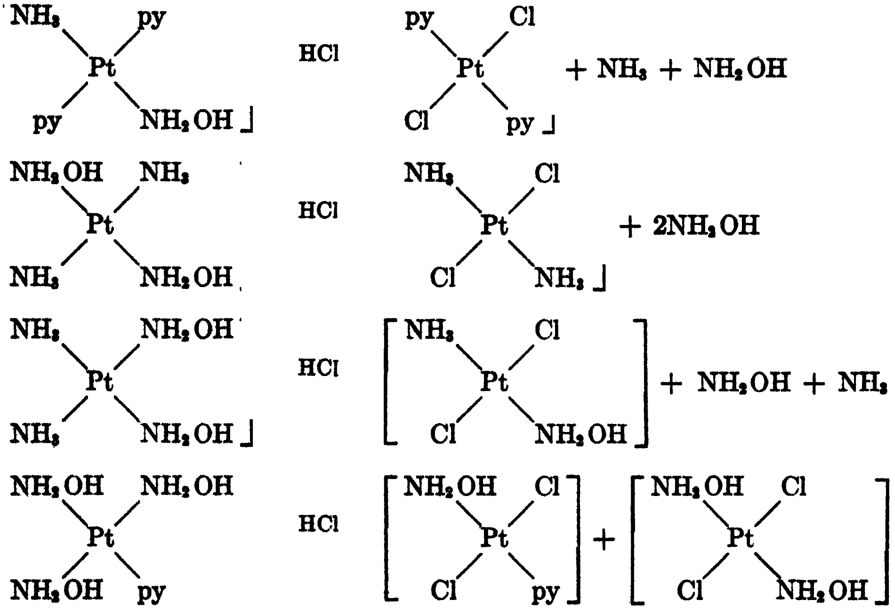
$$[Pt(NH_3)_4]^{++} \xrightarrow{Cl^-} [Pt(NH_3)_3Cl]^{+} \xrightarrow{Cl^-} \underset{\beta}{[Pt(NH_3)_2Cl_2]}$$

$$[PtCl_4]^{--} \xrightarrow{NH_3} [PtNH_3Cl_3]^{-} \xrightarrow{NH_3} [Pt(NH_3)_2Cl_2]$$

If the complexes were tetrahedral it would be impossible to account for the two different end products of these reactions. Let us imagine we have a square complex



into which another X is to be substituted for one of the A's. In what circumstances does the first X group direct the second one entering; to the *cis* position as in [PtNH$_3$Cl$_3$]$^-$ or to the *trans* position as in [Pt(NH$_3$)$_3$Cl]$^+$? At first sight it might seem as though X groups are *trans* directing when present in cationic complexes. Pinkard, Saenger, and Wardlaw (127) have studied very thoroughly the elimination reactions occurring with tetrammines containing ammonia, pyridine, and hydroxylamine, and in every instance the reaction indicates *trans* elimination.



It will be seen that no other X group than Cl was investigated, and as far as the author is aware no systematic work has been done along these lines. However, the behavior of certain nitro palladium compounds is worthy of note. From the evidence available (91) it would seem that the NO$_2$ group is directed to the *cis* position when it enters the complex [Pd(NH$_3$)$_3$NO$_2$]$^+$ and to the *trans* position when it enters the complex [Pd(NH$_3$)(NO$_2$)$_3$]$^-$, which is just the opposite of the behavior of chlorine in the above platinum complexes.

Two examples will suffice to show that the charge on the complex as a whole is not the factor determining directive influences. When $[Pt(NH_3)_2(dipy)]Cl_2$ is treated with hydrochloric acid, the *cis* ammonia molecules are eliminated. This is perhaps hardly a fair test case, because if ammonia molecules are to be eliminated there is no choice but *cis* elimination. A more convincing case is the one discovered by Jensen (71) who, in the course of his dipole-moment investigations, found that when an aqueous solution of K_2PtCl_4 is treated with four molecules of triethylphosphine, a colorless solution of $[Pt\{P(C_2H_5)_3\}_4]Cl_2$ is formed. This solution on standing deposits *cis*-$[Pt\{P(C_2H_5)_3\}_2Cl_2]$ (μ = 10.7 D) and the only way this latter substance can be formed is by *cis* elimination from $[Pt\{P(C_2H_5)_3\}_4]Cl_2$.

B. *Cis* ELIMINATION

The reaction between ammonia and the $[PtCl_4]^{--}$ ion seems typical of many amines. *Cis* elimination from this ion is known to occur with ethylamine, pyridine, hydroxylamine, aniline, etc., but again the reaction is not a perfectly general one. Some very interesting work in this field has been published by Tscherniaev and his school (57, 145). One of their most important findings is that *order* of substitution plays an important part in some complexes. Thus it was found that when ethylene is passed through Cossa's potassium salt, $K[Pt(NH_3)Cl_3]$, *cis*-$[Pt(NH_3)(C_2H_4)Cl_2]$ is formed. On reversing the order of introduction of the groups, i.e., by treating Zeise's salt, $K[Pt(C_2H_4)Cl_3]$, with ammonia, *trans*-$[Pt(NH_3)(C_2H_4)Cl_2]$ is formed. Similar behavior was observed on substituting carbon monoxide for ethylene, but the effects of ordered substitution are confined to unsaturated substances like ethylene and carbon monoxide. It does not, for example, make any difference whether $K[Pt(py)Cl_3]$ is treated with ammonia or $K[Pt(NH_3)Cl_3]$ with pyridine, *cis*-$[Pt(py)(NH_3)Cl_2]$ is the result. Another interesting but less common example of a directive influence is to be found in the complex ions formed with certain optically active diamines like *l*-cyclopentane-*trans*-1,2-diamine (*l*-cptn). Jaeger and ter Berg (69) have shown that any attempt to introduce a second molecule of the dextro base into [Pt(*l*-cptn)Cl_2] fails; the only compounds obtained were D-[Pt(*l*-cptn)$_2$]Cl_2 and L-[Pt(*d*-cptn)$_2$]Cl_2 where, curiously enough, the sign of the rotation of the complex ions is opposite to that of the constituent optically active bases. These authors found no evidence for the existence of the meso form [Pt(*d*-cptn)(*l*-cptn)]Cl_2. In order to describe the curious propeller-like structure of these optically active complex ions, Jaeger and ter Berg have proposed to call them "pterotactic" complexes.

The preceding examples are sufficient to show that the directive influences in substitution in square complexes present an interesting problem for the theoretical chemist.

X. THE UNIVERSALITY OF THE SQUARE STRUCTURE AMONG PLATINOUS COMPOUNDS

It now remains to consider whether the square structure is universal among Pt^{II} compounds and as characteristic of that atom as the tetrahedral structure is of carbon. The cases put to the test in physical investigation are necessarily few in number. As there is now no doubt about the origin of the geometrical isomerism, a better idea of the extent of the occurrence of the square structure can be gained from a brief survey of isomeric forms. Justification for extrapolating to cover all platinous compounds will be found in the quantum theory of the directed valence bond.

VARIETIES OF ISOMERIC SQUARE COMPLEXES

It is a simple matter to draw up a scheme showing the types of isomeric complexes which are possible on the assumption that $\mathrm{Pt^{II}}$ is square coördinated, and it is interesting to see how far these possibilities have been realized in practice. At the same time the scheme will give some idea of the complexity introduced into the chemistry of $\mathrm{Pt^{II}}$ by its habit of forming square bonds. All finite mononuclear complexes of quadricovalent $\mathrm{Pt^{II}}$ must fall into one or other of these classes: (*a*) $[\mathrm{PtA_4}]^{++}$, (*b*) $[\mathrm{PtA_3X}]^{+}$, (*c*) $[\mathrm{PtA_2X_2}]^{\circ}$, (*d*) $[\mathrm{PtAX_3}]^{-}$, (*e*) $[\mathrm{PtX_4}]^{--}$.

In the scheme adopted the following symbols have been used:

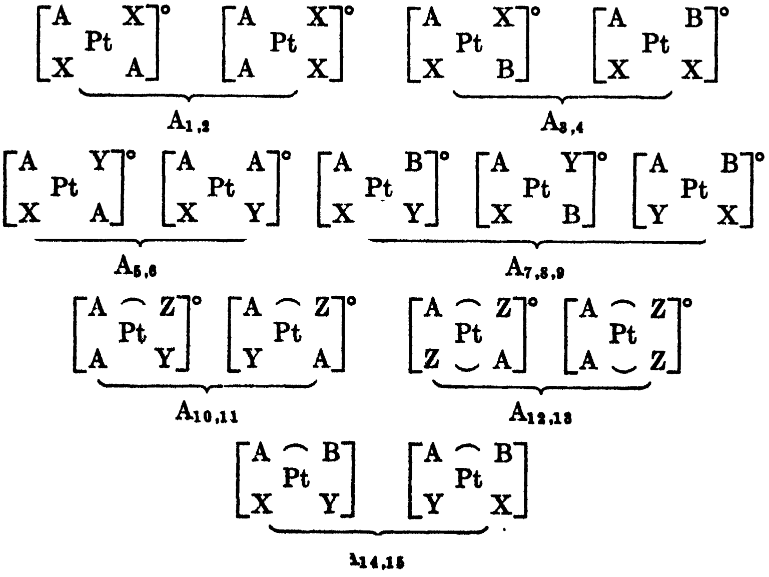
(*1*) A, B, C, etc., to represent neutral molecules, e.g., $\mathrm{NH_3}$, $\mathrm{C_5H_5N}$, $\mathrm{NH_2OH}$, $\mathrm{N_2H_4}$, $\mathrm{CH_3NH_2}$, $\mathrm{C_2H_5NH_2}$, $\mathrm{AsCl_3}$, $\mathrm{P(CH_3)_3}$, $\mathrm{(C_2H_5)_2S}$, etc.

(*2*) AB to represent an unsymmetrical bidentate chelate group attached by two coördinate links, e.g., isobutylenediamine.

(*3*) AZ to represent an unsymmetrical chelate group attached by a coördination link and one primary link, e.g., glycine.

(*4*) X, Y, Z, . . . etc., to represent a negatively charged atom or group such as $\mathrm{Cl^-}$, $\mathrm{CN^-}$, $\mathrm{NO_2^-}$, $\mathrm{OH^-}$, etc.

Class A. Non-electrolyte or uncharged complexes



$A_{1,2}$ $A_{3,4}$ $A_{5,6}$ $A_{7,8,9}$ $A_{10,11}$ $A_{12,13}$ $A_{14,15}$

Examples of Class A are the following:

$A_{1,2}$: *cis*- and *trans*-$[\mathrm{Pt(NH_3)_2Cl_2}]$
$A_{3,4}$: *cis*- and *trans*-$[\mathrm{Pt(NH_3)(py)Cl_2}]$ (77)
$A_{5,6}$: *cis*- and *trans*-$[\mathrm{Pt(NH_3)_2(NO_2)OH}]$
A_7: $[\mathrm{Pt\{(C_2H_5)_2S\}\{(C_2H_5)_2Se\}I, Cl}]$ (121)
$A_{10,11}$: No examples known.
$A_{12,13}$: $[\mathrm{Pt(NH_2CH_2COO)_2}]$ (61)
$A_{14,15}$: No examples known.

Numerous examples of classes $A_{1,2}$ and $B_{1,2}$ have been described throughout the literature. On a rough estimate there must be several hundred examples of isomeric forms of all kinds. (Comprehensive lists are to be found in J. W. Mellor's *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. 16, Longmans, Green and Company, London (1937). and in Gmelin-Kraut's *Handbuch der anorganische Chemie*, Bd. 5, Teil 3, Heidelberg.)

Class B. Divalent cationic complexes

$$\underbrace{\begin{bmatrix} A & & A \\ & \mathrm{Pt} & \\ B & & B \end{bmatrix}^{++} \begin{bmatrix} A & & B \\ & \mathrm{Pt} & \\ B & & A \end{bmatrix}^{++}}_{B_{1,2}} \quad \underbrace{\begin{bmatrix} A & & C \\ & \mathrm{Pt} & \\ B & & A \end{bmatrix}^{++} \begin{bmatrix} A & & A \\ & \mathrm{Pt} & \\ B & & C \end{bmatrix}^{++}}_{B_{3,4}}$$

$$\underbrace{\begin{bmatrix} A & & B \\ & \mathrm{Pt} & \\ C & & D \end{bmatrix}^{++} \begin{bmatrix} A & & C \\ & \mathrm{Pt} & \\ D & & B \end{bmatrix}^{++} \begin{bmatrix} A & & B \\ & \mathrm{Pt} & \\ D & & C \end{bmatrix}^{++}}_{B_{5,6,7}} \quad \underbrace{\begin{bmatrix} A & \frown & B \\ & \mathrm{Pt} & \\ A & \smile & B \end{bmatrix}^{++} \begin{bmatrix} A & \frown & B \\ & \mathrm{Pt} & \\ B & \smile & A \end{bmatrix}^{++}}_{B_{8,9}\,[12]}$$

$$\underbrace{\begin{bmatrix} A & \frown & B \\ & \mathrm{Pt} & \\ C & \smile & D \end{bmatrix}^{++} \begin{bmatrix} A & \frown & B \\ & \mathrm{Pt} & \\ D & \smile & C \end{bmatrix}^{++}}_{B_{10,11}} \quad \underbrace{\begin{bmatrix} A & \frown & B \\ & \mathrm{Pt} & \\ C & & D \end{bmatrix}^{++} \begin{bmatrix} A & \frown & B \\ & \mathrm{Pt} & \\ D & & C \end{bmatrix}^{++}}_{B_{12,13}}$$

Examples of Class B are the following:

$B_{1,2}$: *cis*- and *trans*-$[\mathrm{Pt(NH_3)_2(py)_2}]^{++}$ (77)
$B_{8,9}$: *cis*- and *trans*-$[\mathrm{Pt\{NH_2C(CH_3)_2CH_2NH_2\}_2}]^{++}$ (44)
$B_{10,11}$: *cis*- and *trans*-$[\mathrm{Pt(NH_2CH_2CH_2(C_6H_5)NH_2)(C_{12}H_{12}N\cdot CH_2NH_2)}]^{++}$ (132)
$B_{12,13}$: *cis*- and *trans*-$[\mathrm{Pt(NH_3)(C_2H_5NH_2)\{NH_2C(CH_3)_2CH_2NH_2\}}]^{++}$ (44)

Class C. Monovalent cationic complexes

$$\underbrace{\begin{bmatrix} A & & A \\ & \mathrm{Pt} & \\ B & & X \end{bmatrix}^{+} \begin{bmatrix} A & & B \\ & \mathrm{Pt} & \\ X & & A \end{bmatrix}^{+}}_{C_{1,2}} \quad \underbrace{\begin{bmatrix} A & & B \\ & \mathrm{Pt} & \\ C & & X \end{bmatrix}^{+} \begin{bmatrix} B & & C \\ & \mathrm{Pt} & \\ A & & X \end{bmatrix}^{+} \begin{bmatrix} C & & B \\ & \mathrm{Pt} & \\ A & & X \end{bmatrix}^{+}}_{C_{3,4,5}}$$

$$\underbrace{\begin{bmatrix} A & \frown & B \\ & \mathrm{Pt} & \\ C & & X \end{bmatrix}^{+} \begin{bmatrix} A & \frown & B \\ & \mathrm{Pt} & \\ X & & C \end{bmatrix}^{+}}_{C_{6,7}} \quad \underbrace{\begin{bmatrix} A & \frown & Z \\ & \mathrm{Pt} & \\ B & & C \end{bmatrix} \begin{bmatrix} A & \frown & Z \\ & \mathrm{Pt} & \\ C & & B \end{bmatrix}}_{C_{8,9}}$$

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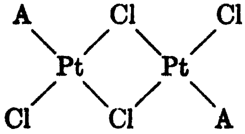
[12] Groups other than unidentate and bidentate have been omitted from this scheme.

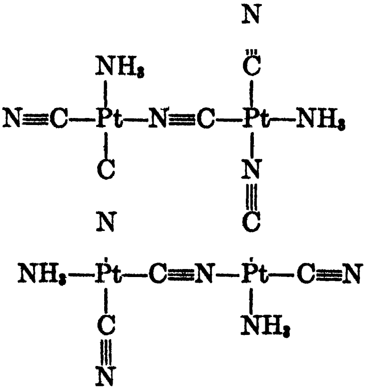
Examples of Class C are the following:

$C_{1,2}$: *cis*- and *trans*-$[Pt(NH_3)_2(NH_2OH)NO_2]^+$ (143, 144)
$C_{3,4,5}$: three isomers of $[Pt(NH_3)(py)(NH_2OH)NO_2]^+$ (143)
No examples of the other classes are known.

A classification along the same lines could be drawn up for anionic classes of the types $[PtX_2Y_2]^{--}$, $[PtX_2YZ]^{--}$ . . . . $[PtAXYZ]^-$, $[PtAX_2Y]^-$, etc., but as only a few examples of isomerism have been recorded in this category and as the classification would simply repeat much of that already given it will not be pursued any further. The scarcity of isomeric forms may well be due to the fact that it is more difficult to make the appropriate substitutions in anionic complexes and also to the fact that the *cis*-forms may not be sufficiently stable. Two substances in this class have, however, been recorded as existing in isomeric forms: namely, $K_2[Pt(S_2O_3)_2]$ (134) and $K_2[Pt(NH_2SO_3)_2Cl_2]$ (79), and no doubt careful search would reveal others. No attempt has been made to draw up a scheme for isomeric polynuclear compounds, mainly because not a single example of isomerism has been found even among those of the simplest type like (1, 72)



Furthermore, the possibilities of isomerism are increased in the more complex polynuclear compounds and few instances of compounds with more than two platinum atoms per molecule have been recorded. The substance with empirical composition $[PtNH_3(CN)_2]_x$, described many years ago by Cleve (22), would probably repay further investigation, since its composition suggests that it may have the following structure:



This survey of isomers would not be complete without some reference to a number of instances where forms in excess of those required by theory have been reported, if only because the existence of these forms has occasionally been used as an argument against the square structure. Jensen (74) has investigated several examples and in each case, except one, he has shown that the alleged third isomer is a mixture of α- and β-forms. The exception noted was the γ-dichlorodiammine of Angell, Drew, and Wardlaw (43) and this proved to be the *trans*-diammine contaminated with a polynuclear complex. No isomers would be expected for the compound [Pt(dipy)Cl_2]; nevertheless a yellow and a red form have been reported. As the two forms are indistinguishable chemically, Morgan and Burstall (114, 115) have set them down as dimorphous forms, a conclusion which could be checked by examining the absorption spectra of each of the two forms in a suitable solvent. If, as the observation that the red form is transformed to the yellow in chloroform solution suggests, there is no difference, there would seem to be little doubt that it is a case of dimorphism. At times it is difficult to find chemical differences between truly isomeric complexes, especially those of the type [Pt$(AX)_2$] and here the absorption test is specially useful, as Lifschitz and Froentjes have shown in their work on the platinous ethyl-thiolactic acid complexes (86).

TABLE 5

CONFIGURATION	NATURE OF EXPERIMENTAL EVIDENCE USED FOR EXCLUDING THE CONFIGURATION
Pyramidal, tetragonal, or rhombic	Dipole moments; Raman and infrared spectra; crystal structure
Tetrahedral (regular)	Geometrical and mirror-image isomerism; Raman and infrared spectra; crystal structure; dipole moments, crystal optics
Bisphenoidal (tetragonal or rhombic)	Mirror-image isomerism; crystal structure; dipole moments
Rectangular	Crystal structure; Raman and infrared spectra

XI. SUMMARY OF EXPERIMENTAL DATA

While the results of the relatively few crystal-structure analyses of platinous compounds must be given great weight, the full force of the argument for the square structure as a general characteristic of Pt^{II} can best be understood from a consideration of the experimental evidence as a whole. This can be most conveniently done by summarizing the data which exclude all but one of the various theoretically possible configurations (table 5). The only reasonable configuration[13] which remains is the square one, and as this can be used to give a consistent explanation of all the observed phenomena it must be considered as established beyond all reasonable doubt.

[13] In the above scheme no provision has been made for the peculiar arrangement of four bonds found in $TeCl_4$ (140) and in the $[IO_2F_2]^-$ ion (67). This configuration is best described as that of a trigonal bipyramid in which one of the three equivalent positions is occupied by an unshared electron pair. It may also be regarded as derived from the tetragonal bisphenoidal configuration by increasing one of the bond angles of the central atom

XII. THEORETICAL EVIDENCE

By the application of general quantum-mechanical principles to the problem of the orientation of chemical bonds Pauling (117) has, on the basis of a single postulate,[14] derived a large number of results of great stereochemical interest. It is perhaps no serious test of the theory of the directed bond that it predicts the square bonding of Pt^{II}, although the general evidence for this latter was not so strong when the theory was first propounded. Nor should it be implied that support for the quantum-mechanical theory of the directed bond comes only from the experimental results dealing with quadricovalent elements. It is, however, necessary to restrict the discussion here to the deductions of the theory relating to such elements. The relevant rules are these: (*1*) Square bonds will be formed whenever dsp^2 orbitals are involved in bond formation. (*2*) Tetrahedral bonds will be formed whenever sp^3 orbitals are involved in bond formation.

Any atom whose structure is such as will permit the use of orbitals, that is any atom with a vacant *d* orbital just within its valence shell, will form square, rather than tetrahedral, bonds, because by so doing a more stable structure will result. The electronic structure of Pt^{II} fulfils just these conditions.

From the numerous examples of square structure already dealt with, and from the above rule, it is a fair inference to conclude that square bonding is as universal among platinous compounds as tetrahedral bonding is among carbon compounds.

NON-PLANAR STRUCTURES

Such an inference does, however, require several qualifications. Firstly, the above bonding rules refer only to electron-pair or covalent bonds. If the difference between the electronegativities of the atoms is sufficiently large, they may be held together by predominantly ionic tetrahedral bonds which do not involve pairing of electrons as in covalent-bond formation. The mere fact of an atom forming square bonds shows that the bonds are covalent, since the configuration of minimum potential energy for four ionic bonds is the tetrahedral one. As will be discussed more fully in the sequel, the magnetic criterion may be used to distinguish between the two bond types. If Pt^{II} formed ionic bonds, i.e., if platinum existed as the Pt^{++} ion in any of its compounds, these should be paramagnetic with susceptibilities corresponding to the presence of two unpaired electron spins. As a matter of actual experience, all platinous compounds examined to date have proved to be diamagnetic, from which we can infer that platinum does not exist in the ionic condition in any of these compounds. About the only likely compounds in which Pt^{II} might be found are those with fluorine, the

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to 180°. It is not, however, a bisphenoidal arrangement. This unusual arrangement of bonds owes its existence to the fact that the unshared electron pair is stereochemically active as in the nitrogen of ammonia, but since there is no parallel between the structures of the valency shells of platinum and tellurium, the configuration has not been included. In any event it is ruled out by the results of Raman spectra and crystal-structure work.

[14] "Of two orbitals in an atom the one which can overlap more with an orbital of another atom will form the stronger bond with that atom and moreover, the bond formed by a given orbital will tend to be in that direction in which the orbital is concentrated" (118).

most electronegative of all elements, but very little is known of such compounds. The few referred to in the literature are by no means well defined, and in no case has any magnetic work been done on them. Nevertheless this possible exception to the general rule must be borne in mind.

Secondly, the bonding rules refer only to compounds in which Pt^{II} has a coördination number four. While this number seems almost universal, there are one or two cases where it may possibly rise to six. Two instances come to mind: The bis(α, β, γ-triaminopropane)platinous ion (90, 92) and the *cis*- and *trans*-forms of bis(acetonitriletetrammine)platinous chloride (147). Doubt has recently been cast on the correctness of the interpretation of the evidence for the last two compounds (83), and in any event all the evidence for octahedral coördination is of a purely chemical nature. Some useful work remains to be done in checking the chemical findings by crystal structure analyses, or by some other means. An octahedral structure has been attributed to $[Pt(NH_3)_4]Cl_2$ (64) but crystal-structure data are definitely against this view.

Finally, it must be emphasized that the quantum-mechanical rules relating to the directed chemical bond refer only to bonds *free to arrange* and that where this condition obtains the bond angles found are very close to those required by theory. Thus, electron-diffraction studies show that in methylene chloride, chloroform, propane, isobutane, and other such molecules the angles between single bonds to carbon are from 109° to 112°, close to the tetrahedral value of 109°28′. Yet there is not the slightest doubt that in cyclopropane the angles between single bonds to carbon are 60°. Permanent bond-angle distortions inherent in the configuration adopted by a molecule are by no means rare (97) and must be allowed for in discussing the stereochemistry of platinum. Crystal-structure analyses reveal bond angles of 90° in $K_2[PtCl_4]$, $[Pt(NH_3)_4]Cl_2$, etc., but there may well arise instances where, under duress, as it were, such large bond-angle distortions may be produced as to alter completely the symmetry of a complex. Two examples of what may be called "forced configurations" will be considered here. The first is the compound β,β',β''-triaminotriethylamineplatinous chloride described by Mann and Pope (93). If platinum is regarded as having a coördination number of four, then it is sterically impossible for it to be square coördinated here (see figure 10).

Platinum might conceivably be octahedrally coördinated in this compound, and without a crystal analysis it is difficult to eliminate this possibility with any degree of certainty. The same objection does not apply to compounds containing bis-3,3′,5,5′-tetramethyl-4,4′-dicarbethoxydipyrromethene (figure 11).

Porter (129) has shown that if this substituted pyrromethene, with methyl groups in the α-positions, functions as a bidentate chelate group,—and the evidence is that with many metals it does,—then any attempt on the part of the chelate to assume a planar configuration is prevented by steric hindrance. The α methyl groups (asterisked in figure 11) must clash. The clashing is more serious than might be gathered from the figure. In redrawing it with the appropriate dimensions (figure 12), the extent of the overlapping of the methyl groups is indicated by horizontal shading. It should be pointed out that, owing to resonance in the pyrrole ring, the α methyl groups and the ring would normally be coplanar. Under stress the methyl groups might be bent to some small extent out of the plane of the pyrrole ring, but because of the large van der Waals'

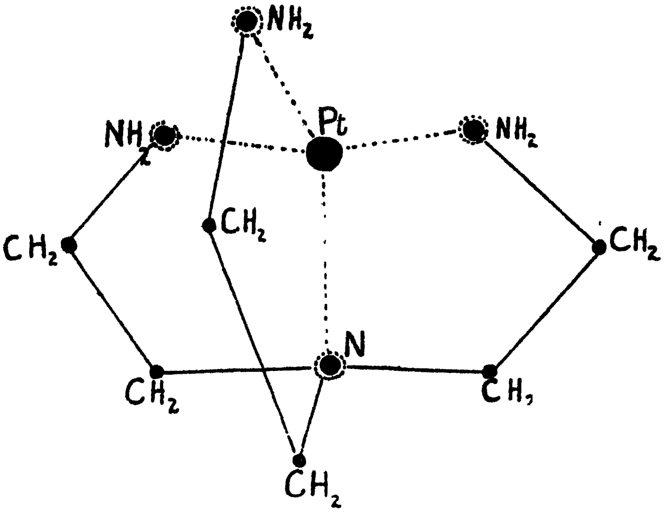

FIG. 10. β,β′,β″-Triaminotriethylamineplatinous chloride

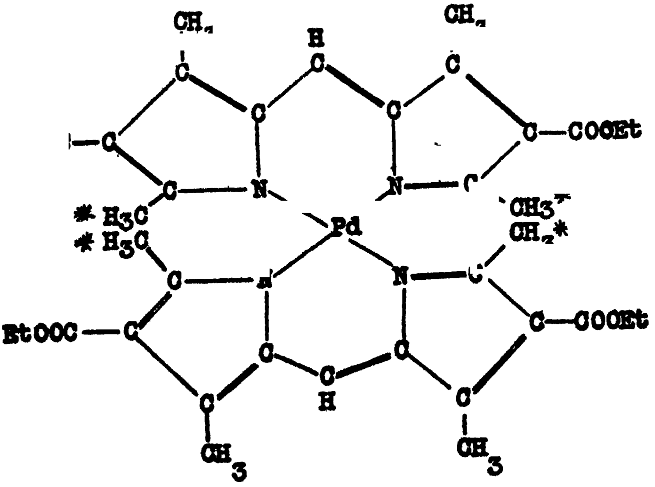

FIG. 11

radius of the methyl group, 2 Å., no amount of distortion of the C—CH_3 could accommodate chelating dipyrromethene groups in square-coördinated positions. By assuming that the methyl groups remain in the plane of the pyrrole rings, and that all the distortion occurs in the CH_2—N bonds, a rough calculation shows that the distortion amounts to about 40° (103).

Although quite a number of metal derivatives of this dipyrromethene have been described, curiously enough the platinum derivative does not appear among them. However, the palladium compound has been prepared (104, 129) and there is little doubt that platinum can also form a compound.

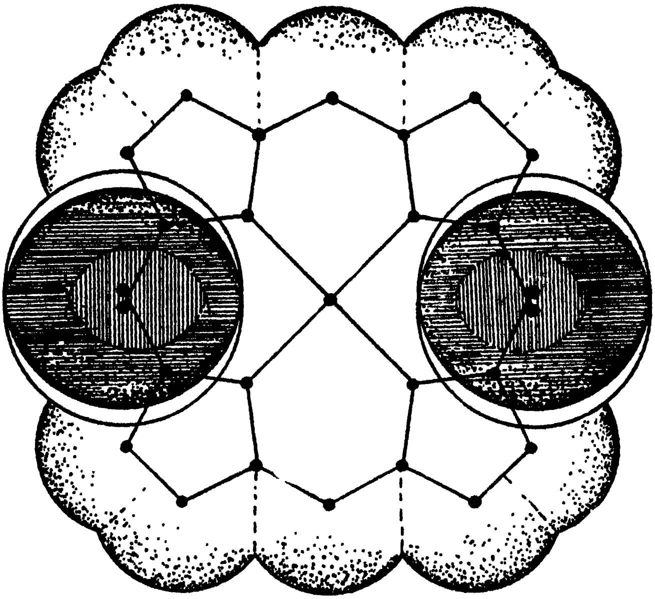

Fig. 12

XIII. Incidence of tne Square Configuration among Other Metal Complexes

The metals for which square coördination is theoretically possible are those whose electronic structures permit the use of dsp^2 orbitals in bond formation, that is to say, those which have a vacant d orbital within the valence shell. The elements which fulfil this condition are confined to the three transition series of the Periodic Table. Table 6, drawn up primarily (120) to show the magnetic moments predicted for the transition elements in different stereochemical configurations, will be used as a basis for discussion. This table is taken (modified) from the paper by Pauling and Huggins (120). It should be explained that the magnetic dipole moment of an atom arises from the existence in it of unpaired electron spins; the magnitude of the moment, in Bohr magnetons (the units employed in the table), is given by the expression $\mu = \sqrt{n(n + 2)}$, where n is the number of unpaired spins. For diamagnetic substances $n = 0$.

Several interesting features of table 6 call for comment. In the first place it will be seen that the magnetic distinction between ionic, tetrahedral, and square coördination can be made only with elements in horizontal rows 6, 7, 8, and 9. Secondly, although square coördination is theoretically possible with any element of the three transition series, it has actually been found with very few (shown in heavy type), and these are confined to the relatively small portion of the table marked off with a heavy line. It is significant that the square structure is most common among elements with zero or one unpaired electrons ($\mathrm{Pt^{II}}$, $\mathrm{Pd^{II}}$, $\mathrm{Au^{III}}$, $\mathrm{Ni^{II}}$, $\mathrm{Co^{II}}$, $\mathrm{Cu^{II}}$, $\mathrm{Ag^{II}}$), very rare or doubtful among those with two or three ($\mathrm{Fe^{II}}$, $\mathrm{Mn^{II}}$), and, as far as is known, non-existent among those with the maximum number possible, four. The numbers of unpaired electrons just quoted refer of course to the different atoms in the square-coördinated condition. The same tendency to assume configurations with small numbers of unpaired electrons is to be seen among the diamagnetic complexes of Co, Pt, Pd, and Ir, which are invariably octahedral.[15] These observations may be summarized in a general rule which states that, when a metal atom of the transition series forms a covalent complex, it tends to assume that configuration (tetrahedral, square, octahedral, etc.) which involves the least possible number of unpaired electrons.

TABLE 6

Predicted magnetic moments of complexes containing transition elements

	THE IRON GROUP	THE PALLADIUM GROUP	THE PALATINUM GROUP	NUMBER OF ELECTRONS IN *d* SHELL (3*d*, 4*d*, OR 5*d*)	FOR IONIC OR sp^3 (TETRAHEDRAL) BONDS	FOR FOUR dsp^2 (SQUARE) BONDS	FOR SIX d^2sp^3 (OCTAHEDRAL) BONDS
1	$\mathrm{K^{I}Ca^{II}Sc^{III}Ti^{IV}}$	$\mathrm{Rb^{I}Sr^{II}Y^{III}Zr^{IV}}$ $\mathrm{Nb^{V}Mo^{VI}}$	$\mathrm{Cs^{I}Ba^{II}}$–$\mathrm{Hf^{IV}Ta^{V}}$ $\mathrm{W^{VI}}$	0	0.00	0.00	0.00
2	$\mathrm{V^{IV}}$	$\mathrm{Nb^{IV}Mo^{V}}$	$\mathrm{W^{V}}$	1	1.73	1.73	1.73
3	$\mathrm{V^{III}Cr^{IV}}$	$\mathrm{Mo^{IV}Ru^{VI}}$	$\mathrm{W^{IV}Os^{VI}}$	2	2.83	2.83	2.83
4	$\mathrm{V^{II}Cr^{III}Mn^{IV}}$	$\mathrm{Mo^{III}}$		3	3.88	3.88	3.88
5	$\mathrm{Cr^{II}Mn^{III}Fe^{IV}}$	$\mathrm{Mo^{II}Ru^{IV}}$	$\mathrm{Os^{IV}}$	4	4.9	4.9	2.83
6	$\mathrm{Mn^{II}Fe^{III}Co^{IV}}$	$\mathrm{Ru^{III}}$	$\mathrm{Os^{III}Ir^{IV}}$	5	5.91	3.88	1.73
7	$\mathrm{Fe^{II}Co^{III}}$	$\mathrm{Ru^{II}Rh^{III}Pd^{IV}}$	$\mathrm{Ir^{III}Pt^{IV}}$	6	4.90	2.83	0.00
8	$\mathrm{Co^{II}Ni^{III}}$	$\mathrm{Rh^{II}}$	$\mathrm{Ir^{II}}$	7	3.88	1.73	
9	$\mathrm{Ni^{II}}$	$\mathrm{Rh^{I}Pd^{II}Ag^{III}}$	$\mathrm{Pt^{II}Au^{III}}$	8	2.83	0.00	
10	$\mathrm{Cu^{II}}$	$\mathrm{Ag^{II}}$		9	1.73		
11	$\mathrm{Cu^{I}Zn^{II}Ge^{IV}}$	$\mathrm{Ag^{I}Cd^{II}In^{III}}$	$\mathrm{Au^{I}Hg^{II}Ti^{III}Pb^{IV}}$ $\mathrm{Bi^{V}}$	10	0.00		

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[15] If the results of the incomplete x-ray study (34) of $\mathrm{Pt(CH_3)_3Cl}$ are correct, this compound should have a magnetic moment of 4.9 Bohr magnetons, which, in view of the data so far available for platinum compounds, is very unlikely. Platinum is most likely octahedrally coördinated in this compound, as in $\mathrm{Pt(CH_3)_4}$ (118).

The usefulness of a theory is determined largely by the extent to which its predictions check satisfactorily with experiment. In this respect the quantum theory of the directed valence bond has fared well. For example, it predicted (117) that the diamagnetic complexes of Ni^{II} and Au^{III} would have the square structure; in both instances crystal analyses and other investigations have amply borne this out.

Where definite evidence for square coördination has been found for any element it may be assumed that it will be found in this condition generally, unless (*1*) the element is octahedrally coördinated, (*2*) steric effects cause bond-angle distortion, (*3*) marked electronegativity differences produce predominantly ionic (tetrahedral) binding. It is true that some elements, notably Fe^{II} and Mn^{II}, are so very sensitive to this last factor that they are seldom square coördinated. On the other hand, the above provisos rarely have to be invoked for Pt^{II}, Pd^{II}, Cu^{II}, and Au^{III}.

XIV. SQUARE-COMPLEX FORMATION WITH METALS OTHER THAN PLATINUM

A. PALLADIUM

This element resembles platinum very closely except in one respect. Neither the geometrical nor the optical isomers of Pd^{II} retain their configurations with the same tenacity as those of Pt^{II}. Geometrical isomerism is confined, so far as the observations go, to neutral complexes. In summarizing the evidence for Pd^{II} and the metals to follow, the nature of the investigation will first be indicated and then the compound in which the square structure has been found.

Crystal structure: $K_2[PdCl_4]$ (38, 142); PdO (87); $[Pd(NH_3)_4]Cl_2$ (37); $K_2[Pd(COS)_4]$ (32); $[((CH_3)_2S)_2PdCl_2]$ (27); PdS (54); $PdCl_2$ (151); $[((CH_3)_3As)_2PdBr_2]$ (95); $[(NH_3)_2Pd(C_2O_4)]$ (91).

Geometrical isomerism: Cis- and *trans*-forms of benzylmethylglyoximepalladium (46); *cis-* and *trans*-bisglycinepalladium (98, 128); *cis-* and *trans*-dichlorodiamminepalladium (62); *cis-* and *trans*-$[(NH_3)_2Pd(NO_2)_2]$ (91).

Optical isomerism: Isobutylenediaminestilbenediaminepalladous salts (84).

Dipole moments: $[PdCl_2(AsR_3)_2]$ (94); $[PdCl_2((C_2H_5)_3Sb)_2]$ (73).

Crystal optics: $K_2[PdCl_4]$ (98); $Ba[Pd(CN)_4]4H_2O$ (12), etc.

Magnetic susceptibilities: $K_2[PdCl_4]$, etc. (70).

B. NICKEL

This is the first element so far considered for which there is evidence of both the square and tetrahedral configuration, although it must be admitted that the evidence for the latter is as yet rather meager. Theory predicts a square covalent structure for diamagnetic, and an ionic tetrahedral structure for paramagnetic complexes. The former prediction has been abundantly verified, as the following summary shows:

Crystal structure: $K_2[Ni(COS)_4]$ (32); $Ba[Ni(CN)_4]4H_2O$ (13); $Na_2[Ni(CN)_4]3H_2O$ (15); bis(*N*,*N'*-dipropyldithiocarbamate)nickel (125).

Geometrical isomerism: Bis(methylglyoxime)nickel (146); bis(benzylmethylglyoxime)nickel (141); bis(thiosemicarbazide)nickelous sulfate (75); nickel salicylaldimine (81).

Dipole moments: $[NiBr_2((C_2H_5)_3P)_2]$ ($\mu = 0$) and related compounds (73); nickel glyoximes (20); nickel salicylaldimine (81).

Crystal optics: $K_2[Ni(CN)_4]$ (107); $Ba[Ni(CN)_4]$ (12), etc.

Magnetic susceptibilities: Nickel ethyldithiocarbamate, etc. (19); a wide range of nickel complexes (102); bis(phenylethylenediamine)nickel chloride, etc. (85).

All the compounds mentioned above are diamagnetic. On the assumption that the magnetic criterion for distinguishing configurations is valid, a study (102) has been made of the factors which determine whether nickel will be tetrahedrally or square coördinated. This study shows that differences between the electronegativity of the nickel and the atoms linked to it play a major rôle; if these differences are large, the bonds are predominantly ionic in character and the structure is tetrahedral. All complexes in which Ni^{II} is bound to four oxygen atoms, as in bis(salicylaldehyde)nickel for example, are paramagnetic. There is also evidence that extensive deflection of bond directions, which in the absence of steric influences would be expected to assume the square orientation, results in a marked change of bond character (104). The bond changes from one of predominantly covalent character to one of predominantly ionic character. The difference in stability of the two configurations must at times be relatively small, as there are instances where the one complex may under some conditions be diamagnetic and under other not very different conditions paramagnetic (85, 86). A notable characteristic of diamagnetic nickel compounds is that they show little tendency to assume sixfold coördination. Paramagnetic nickel compounds with a coördination number of four, on the other hand, quite readily take up two additional atoms or groups to assume the octahedral configuration (47).

It is very interesting to note a similar kind of behavior in ionic Fe^{II} complexes with coördination number four (ferrohemoglobin, etc.), where the change to a diamagnetic octahedral covalent Fe^{II} complex can be readily brought about. The metals which easily form square bonds could not well play the same rôle as Fe^{II} in the blood pigments.

Paramagnetic and diamagnetic nickel compounds lend themselves to studies on the correlation between bond character and absorption spectrum and one or two interesting results have been reported (109). The method of procedure was to compare the absorption of a nickel organic coördination compound with that of the organic molecule from which it was derived, comparisons being made in the same solvent throughout. A marked difference in the two magnetic types was found. Thus, diamagnetic complexes in which the four atoms linked to nickel are two oxygen and two nitrogen atoms exhibit the following features: (*a*) bands of the coördinated molecule, slightly displaced, usually to longer wave lengths; (*b*) one or more bands[16] of appreciable intensity (sometimes with a molecular extinction coefficient approaching 7000) not found in the metal-free molecule. These latter bands must be attributed to the presence of the nickel atom in the complex. On the other hand, in the range 6500 to 2500 Å., paramagnetic complexes of nickel show no band, or at least no band of appreciable intensity comparable to (*b*) above, which can be attributed to nickel. Only a relatively limited range of complexes has been examined so far and it is therefore premature to make any generalization.

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[16] French, Magee, and Sheffield (52) state that one band only was found by Mills and Mellor, but two bands were actually recorded for both bis(salicylaldoxime)nickel and ethylenediamine-formylcamphor nickel, the weaker having a maximum at 6200 Å. (109).

The tetrahedral configuration for Ni^{II}

Apart from magnetic data, the evidence which has been brought forward to prove the existence of this alternative structure is confined to two lines of approach. There is first of all Jensen's observation (75) that paramagnetic $[Ni((C_2H_5)_3P)_2(NO_3)_2]$ has a large electric dipole moment which presumably arises from a tetrahedral arrangement of the attached groups rather than from the less stable *cis*-planar arrangement. Secondly, there are the data of French and Corbett (51) on the rotatory dispersion and absorption of paramagnetic nickel formylcamphor. The argument used here was that since nickel formylcamphor showed the Cotton effect in a band (maximum at 3172 Å.), the nickel atom must be a center of asymmetry and therefore tetrahedrally coördinated. From the work of Mills and Mellor (109) there is some doubt as to whether the band at 3172 Å., in which the Cotton effect occurs, can be attributed to the presence of nickel atom in the complex.

In any event it has been shown (97) that ethylenediamine-formylcamphor nickel, which is diamagnetic in the solid state, also shows the Cotton effect in a band (maximum 6200 Å.) which definitely arises from the presence of the nickel atom, since it is absent from the ethylenediamine-formylcamphor itself. From the regularities noted earlier (109) this band is to be associated with covalently bound nickel. French, Magee, and Sheffield (52) have recently reported that ethylenediamine-formylcamphor nickel when dissolved in methyl alcohol is paramagnetic with a moment of 1.9 Bohr magnetons, an observation which must mean that there is an equilibrium between nickel in the two different magnetic conditions.[17] An added complication arises from the fact that some of the nickel may become octahedrally coördinated, in which case it would be magnetically indistinguishable from ionically bound nickel. Although it is unlikely that nickel becomes octahedrally coördinated by the attachment of two ethyl alcohol molecules, it has yet to be shown that the optical effects under discussion are due to tetrahedrally coördinated nickel.

C. GOLD (Au^{III})

In the trivalent condition gold undoubtedly forms square bonds, but it is extremely doubtful whether it does so in the monovalent condition. Further work substantiating the claims of Dothie, Llewellyn, Wardlaw, and Welch (39) is needed before it can be accepted that Au^{I} can be grouped with Au^{III}.

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[17] Attempts have been made to repeat the observation in this laboratory but the solubility of the compound in methyl alcohol is so small that the difference between the magnetic susceptibility of solvent and solution could not be measured with any accuracy. Ethylenediamine-formylcamphor nickel is much more soluble in pyridine, but even in this solvent the susceptibility of the compound did not appear to be very different from its value for the solid (99).

It is noteworthy that no geometrically isomeric auric compounds have been observed, in spite of the definite searches made for them.

Crystal structure: $K[AuBr_4]2H_2O$ (36); $[C_2H_5AuBr_2]_2$ (16); $[(C_3H_7)_2AuCN]_4$ (126); $Cs_2Au_2Cl_6$ (50).

Crystal optics: $[N(C_2H_5)_4][AuCl_4]$, $K[AuBr_4]2H_2O$ (107).

D. SILVER (Ag^{II})

The only instance so far described is argentic picolinate. An incomplete x-ray analysis of this substance made by Cox, Wardlaw, and Webster (33) shows the presence of square complexes.

E. COPPER (Cu^{II})

An outstanding characteristic of copper is that it is much less sensitive to electronegative differences (from a stereochemical viewpoint) than its close neighbors like Ni^{II}, Co^{II}. Several hydrated salts of copper are known, from crystal analyses, to form square complexes, e.g., $CuCl_22H_2O$, $K_2CuCl_42H_2O$, and $CuSO_45H_2O$. No diamagnetic hydrated nickel chloride or sulfate has been reported.

It is very doubtful whether any tetrahedral cupric complexes have yet been found. Arguing by analogy, Mills and Gotts (110) concluded that cupribenzoylpyruvic acid had a tetrahedral structure. It is practically certain that the analogy does not hold.

Large numbers of internal copper complexes containing unsymmetrical chelate groups have been described throughout the literature, and it is extraordinary that so few geometrical isomers have been discovered. One can only conclude that *cis*-isomers must be so unstable as to be incapable of existing for any length of time, or that no special efforts have been made to isolate isomeric forms.

Crystal structure: $CuCl_22H_2O$ (65); $K_2CuCl_42H_2O$ (21); copper diketone (35); $CuSO_45H_2O$ (8); CuO (148); $Cu(py)_2Cl_2$ (28).

Geometrical isomerism: $[Cu_2Cl_3\{(Ph_2Me)_3As\}_3]$ (100); cupric polymethylene bis-imino-acid complexes (138); cupric picolinate (33).

F. COBALT (Co^{II})

The only evidence to date comes from magnetic susceptibility measurements which show that certain internal complexes have a moment corresponding to the existence of one unpaired electron, the number to be expected for a square structure. Magnetic data show that α- and β-$Co(py)_2Cl_2$ are not square forms.

Magnetic susceptibilities: Bis(benzildioxime)cobalt (18); many other internal complexes (103); $[Co(py)_2Cl_2]$ (7, 101).

G. RHODIUM (Rh^{II})

All attempts to prepare square rhodous complexes have so far resulted in failure (99), but Dwyer and Nyholm (48) have described a number of complexes of bivalent rhodium in all of which the Rh^{II} appears to be octahedrally coördinated. They are, without exception, diamagnetic (98).

H. IRON (Fe^{II}) AND MANGANESE (Mn^{II})

Many compounds have been examined (99) in the hope of finding evidence for the square configuration, but without success. Such compounds appear to be very rare, and the only ones reported to date are ferrous and manganous phthalocyanine (139). Several years ago, Cox, Shorter, Wardlaw, and Way (31), on the basis of a determination of unit-cell dimensions, reported that manganous dipyridine chloride $[Mn(py)_2Cl_2]$ had the *trans* square structure. This was subsequently shown to conflict with the magnetic data, which indicated that manganese in this compound was definitely in the ionic condition (101). An alternative octahedral structure was suggested as a way of explaining the small cell dimensions. The structure attributed to the $Mn(H_2O)_4^{++}$ ion in $K_2Mn(SO_4)_24H_2O$ (3) is almost certainly incorrect.

I. IRIDIUM, OSMIUM, AND RUTHENIUM

As already pointed out, iridium, platinum, and palladium, etc. in the higher valence states are invariably octahedrally coördinated. It is only in the lower valence states, as in IrCl, for example, that iridium is likely to have the square structure. The empirical composition of diamagnetic Ir^{II} compounds suggests a coördination number of six for iridium even in this low valence state (99). It seems very unlikely that square structures will be found for Os^{II} and Ru^{II}, since the general tendency among platinum metals is to form complexes with the lowest possible magnetic moments. The predicted magnetic moment for square complexes of Os^{II} and Ru^{II} is 2.83 Bohr magnetons. In practice it is found that the compounds of Os^{II} and Ru^{II} are diamagnetic and have a coördination number of six. It should be mentioned, however, that the diamagnetism of compounds of Rh^{II} and Ir^{II} does not accord with the moments predicted for these atoms in table 6 and that there is other evidence for the breakdown of the predictions for heavy atoms like those of the platinum metals (98).

J. ELEMENTS OUTSIDE THE TRANSITION SERIES

Before concluding this survey, some reference must be made to cases where square coördination has been claimed for atoms not listed in table 6 as capable of forming dsp^2 bonds. The evidence for square Tl^I and Au^I (30) rests mainly on the smallness of one of the dimensions (39) of the unit cell in certain of their compounds and cannot therefore be considered as very satisfactory. With regard to earlier claims relating to a square structure for Cd^{II} (11) and Sn^{II} (29), all that need be said here is that the most recent crystal-structure analyses show that these elements are octahedrally coördinated (89).

It was once believed that the α- and β-forms of $[Te(CH_3)_2I_2]$ were *cis–trans* planar isomerides (149), but Drew (40) claims to have shown this explanation to be untenable. The β-form is said to be a molecular compound: $[TeMeI_3]$ $[TeMe_3I]$. Nevertheless, if the bond orientation discovered by Stevenson and

Schomaker (140) in $TeCl_4$ occurs also in $[Te(CH_3)_2I_2]$, as it most probably does, then it is theoretically possible for the latter compound to exist in three geometrically isomeric forms. It would be interesting to know whether it is possible to synthesize isomeric forms of the appropriate compounds of tellurium (and possibly also selenium and arsenic) in which the unshared electron pair of these atoms is stereochemically active.

Lastly, there is an element outside the transition series which does form bonds directed to the corners of a square but not through the agency of dsp^2 orbitals. In the complex ion $[ICl_4]^-$ (112) the iodine atom has two stereochemically active unshared electron pairs in octahedral positions, a structure, which so far as is known at present, is unique.

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NOTE FROM THE EDITOR

It has been brought to the attention of the editors that certain parts of the article by R. Gilchrist entitled "The Platinum Metals" (Volume **32**, pages 277–372 (1943)) are very similar to and in some cases identical with statements which have appeared previously.

It should be noted particularly that certain portions of pages 343, 344, 345, 346, 347, 348, and 349 were taken from *Modern Aspects of Inorganic Chemistry* by H. J. Emeléus and J. S. Anderson, published by D. Van Nostrand Co., New York, 1938. It is not deemed necessary at the present time to list all of these parts in detail, since it is often difficult to decide when quotation marks should have been used. However, most of the material on page 329 and on pages 334–336 was taken wholly or largely from the above-mentioned book and should have been placed in quotation marks. Reference was made in the text to the book by Emeléus and Anderson but it was not clearly indicated that some of the material was quoted almost verbatim from that book.

W. A. NOYES, JR.

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THE STRUCTURE AND ESTIMATION OF NATURAL PRODUCTS FUNCTIONALLY RELATED TO NICOTINIC ACID

C. A. ELVEHJEM AND L. J. TEPLY

Department of Biochemistry, University of Wisconsin, Madison, Wisconsin

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The authors have attempted to list in this review most of the compounds chemically related to nicotinic acid and to indicate the biological activity of each compound. The importance of the active compounds in animal and bacterial metabolism is outlined. A summary is given of the chemical, physical biological, and microbiological methods available for the determination of nicotinic acid, nicotinamide, and coenzymes I and II: The application of these methods in nutritional and biological studies is discussed briefly.

Ten years ago little attention was given to the chemistry or biochemistry of nicotinic acid and related compounds. In 1934 nicotinamide was characterized as one of the hydrolysis products from coenzymes I and II, and in 1937 both the acid and the amide were shown to be active in the cure and prevention of canine blacktongue and human pellagra. These discoveries naturally stimulated a great deal of interest in the structure and estimation of these compounds in living matter. Much of the information is now fairly extensive, although more work is needed before a complete picture can be presented. It is the purpose of this review to summarize the most important developments during the past six years.

I. HISTORICAL

The first chemical production of nicotinic acid is credited to Huber. In 1867 he (58) obtained from nicotine, by oxidation with sulfuric acid and potassium dichromate, a compound which had the formula $C_6H_5NO_2$, but he did not recognize it as pyridinecarboxylic acid until 1870 (59). The term "nicotinic acid" was apparently used first by Weidel (158), who by the oxidation of nicotine with nitric acid produced a compound which he assumed to have the composition $C_{10}H_8N_2O_3$. Later Laiblin (86) showed that this compound was pyridinecarboxylic acid and that it was identical with the compound made by Huber. In 1879 Weidel (159) produced the same compound from β-picoline and thus demonstrated that nicotinic acid is β-pyridinecarboxylic acid.

Almost fifty years elapsed before nicotinic acid was isolated from natural products. Suzuki, Shimamura, and Odake (139) isolated the compound from rice polishings. Funk (47) isolated nicotinic acid from both yeast and rice polishings but found the acid itself to display no activity in curing pigeon beriberi. Vickery (144) isolated it from yeast without previous hydrolysis and suggested therefore that it was present in the free state.

In 1934 Warburg and Christian (154) isolated nicotinamide from coenzyme II and demonstrated its function as part of a hydrogen-transporting coenzyme (157). Shortly thereafter, Euler, Albers, and Schlenk (33) obtained nicotinamide from coenzyme I, and it was shown that both coenzymes were nicotinamide-adenine-dinucleotides, but that coenzyme II contained three molecules of phosphoric acid while cozymase or coenzyme I contained two. Kuhn and Vetter (84) also prepared nicotinamide from heart muscle.

These studies stimulated further interest in the possible nutritional significance of the acid and the amide. Williams (163) in 1917, impressed by the common occurrence of nicotinic acid and the antineuritic vitamin in several natural substances, again tested nicotinic acid and trigonelline, as well as other pyridine derivatives, for antineuritic potency but found that none of them caused any permanent improvement in polyneuritic fowls. Szymanska and Funk (141) attributed an appetite-stimulating and weight-preserving action to nicotinic acid and the amide. Again in 1937, Funk and Funk (48) found a larger food intake and better growth in rats and pigeons on certain diets when given the acid and especially the amide. Frost and Elvehjem (46) also observed a growth stimulus from nicotinic acid when fed with adenylic acid to rats on purified diets.

In 1936 Koehn and Elvehjem (72) prepared from liver a concentrate which was free of riboflavin and which was highly active in the cure of a chick dermatitis and canine blacktongue. Further purification gave concentrates which contained very small amounts of solid matter, and finally Elvehjem, Madden, Strong, and Woolley (31) demonstrated the activity of nicotinic acid in the cure of blacktongue and isolated nicotinamide from the concentrates. The activity of nicotinic acid in the treatment of blacktongue was soon verified by a number of workers (22, 126, 135). The first report of its successful use in human pellagra was made by Spies, Cooper, and Blankenhorn, and by Fouts in November 1937 (see reviews by Elvehjem (30) and Smith (128)). It is estimated that 400,000 pounds of nicotinic acid will be manufactured in 1943 for therapeutic use and for the fortification of foods.

In 1937 Knight (69) found that nicotinic acid was an essential growth factor for *Staphylococcus aureus* and that nicotinic acid was present in the active preparations of the *Staphylococcus* growth factor. Mueller (99) showed that nicotinic acid is essential for diphtheria bacillus, Koser, Dorfman, and Saunders (78) for dysentery bacillus, and Fildes (44) for *Proteus*. These studies established the importance of nicotinic acid in bacterial metabolism.

STRUCTURE AND PROPERTIES

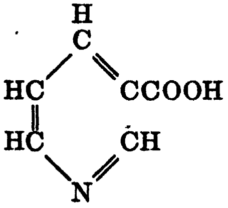
A. NICOTINIC ACID AND COMPOUNDS CLOSELY RELATED TO ITS METABOLISM

1. *Nicotinic acid:* $C_6H_5NO_2$; *molecular weight, 123; melting point, 235–237°C.*

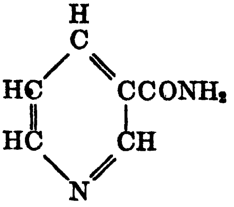
Nicotinic acid occurs as white needle-like crystals or as a crystalline powder. It is soluble to the extent of 1 g. per 60 cc. of water or 80 cc. of alcohol at 25°C. and is freely soluble in hot water and hot alcohol. It is a comparatively weak acid: $pK_a = 4.76$. It is not destroyed by boiling acid or by alkali.

2. *Nicotinamide:* $C_6H_6N_2O$; *molecular weight, 122; melting point, 129–131°C.*

Nicotinamide is a white crystalline powder with a slightly acid taste. It is soluble at 20°C. in two parts of water, four parts of 86 per cent alcohol, eight parts of glycerol, and twenty parts of acetone. It is slightly soluble in ether and insoluble in benzene. Its aqueous solution is slightly alkaline (pH 8.0). Nicotinamide is hydrolyzed to nicotinic acid on heating with strong alkali or acid.



Nicotinic acid



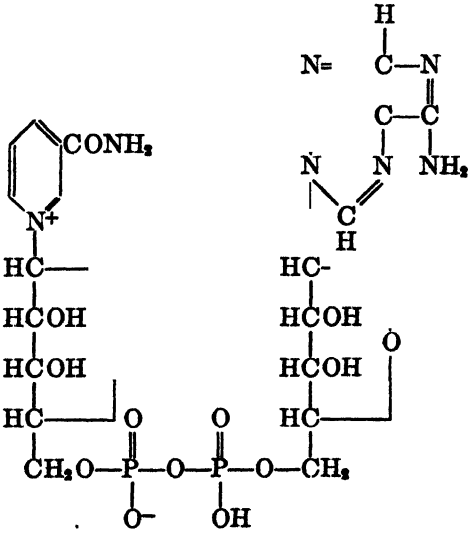
Nicotinamide

3. *Coenzyme I:* $C_{21}H_{27}N_7O_{14}P_2$; *molecular weight, 663*

This coenzyme (diphosphopyridine nucleotide; cozymase) is widely distributed in nature but it is generally prepared from yeast. Several different procedures have been used, and the details of these methods have been reviewed by Schlenk (119). About 0.5 g. of the pure compound is obtained from 10 kg. of yeast. The final product is not crystalline and probably not entirely pure.

In pure form cozymase is colorless and readily soluble in water. It titrates as a monobasic acid. The isoelectric point is at pH 3.1.

The following structure was proposed for cozymase by Schlenk and Euler (123) in 1936, and the final step in verifying this structure has recently been published by Schlenk (122). Adenine was demonstrated in the molecule by Euler and Myrbäck (39), and later Warburg and Christian (155) and Euler, Albers, and Schlenk (34) showed cozymase to be a dinucleotide with one purine (adenine) and one pyridine (nicotinamide) nucleus. The carbohydrate appeared to be

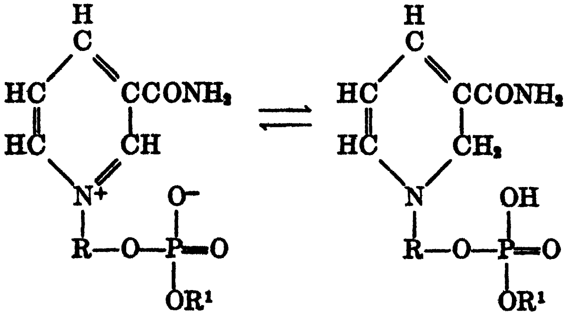


Coenzyme I; cozymase

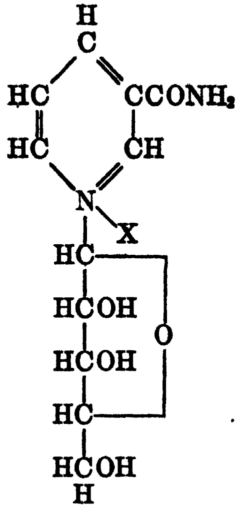
pentose, since inosinic acid was obtained upon deamination. Schlenk (120) obtained 2 moles of pentosephosphoric acid per mole of cozymase and Euler, Karrer, and Becker (37) showed that the phosphoric acid is linked to the ribose in the 5-position. The existence of a pyrophosphate linkage in cozymase was established by the isolation of adenosinediphosphoric acid after alkali treatment.

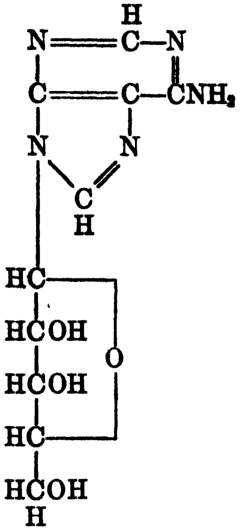
Another problem concerned the linkage between nicotinamide and the rest of the molecule. Warburg (155) showed that in the case of coenzyme II the nicotinamide reacts with two atoms of hydrogen in the presence of a suitable substrate and an active enzyme to form a dihydro compound. This reaction can also be produced with hydrosulfite in slightly alkaline medium. The oxidized form of cozymase has a maximum absorption of 260 mμ but after reduction the intensity at 260 mμ is somewhat reduced and a new maximum appears at 340 mμ. Thus the center of the coenzyme activity resided in the nicotinamide nucleus. The type of linkage between nicotinamide and the rest of the molecule was established by Karrer and his coworkers (67). It was found that nicotinamide iodomethylate showed the same light absorption, fluorescence, and color upon reduction and reoxidation as cozymase and coenzyme II showed. These results indicated that the nicotinamide is found as a quaternary pyridinium base. The free nicotinamide with tertiary nitrogen is not reduced by $Na_2S_2O_4$, in contrast to cozymase, the iodomethylate, and trigonelline, which is the methylbetaine of nicotinic acid. The preparation of nicotinamide derivatives containing carbohydrate radicals on the ring nitrogen gave compounds which showed properties more like those of the coenzyme (66). Tetraacetylglucosidonicotinamide bromide was prepared in pure form, but attempts to prepare the arabinose and xylose derivatives gave only oily products. The model nucleoside not only showed the same optical properties as the coenzyme but showed the same degree of stability to alkali.

When the pyridinium model compounds are reduced to the dihydro compounds, the ring nitrogen of the reaction products become trivalent and they do not contain the acid group. The phosphoric acid in the coenzyme corresponds to the acid group in the model compounds. Upon reduction an acid group is liberated, as follows:



Finally Schlenk was able to obtain nicotinamide nucleoside from cozymase. Since treatment of the coenzyme with either acid or alkali breaks the linkage between nicotinamide and the pentose, it was necessary to resort to the use of a specific phosphatase. The enzymatic hydrolysis gave the two nucleosides.





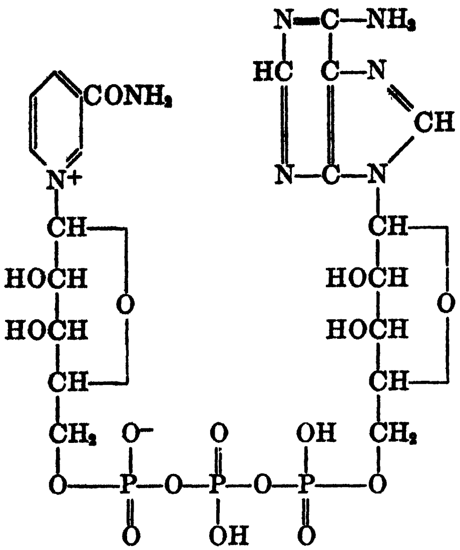
The nicotinamide nucleoside had properties very similar to those of the model compounds prepared by Karrer. Schlenk (122) and Euler, Karrer, and Usteri (38) have definitely proven that the carbohydrate group is ribose. Schlenk also confirmed the earlier investigations that showed that both of the ribosephosphoric acid molecules of cozymase have the phosphoric acid radical linked to carbon atom 5 of the pentoses.

The structure as proposed in 1936 is therefore clearly established; however, the compound has not been synthesized.

4. Coenzyme II: $C_{21}H_{28}N_7O_{17}P_3$; *molecular weight, 743*

Although coenzyme II (triphosphopyridine nucleotide) is as widely distributed in nature as coenzyme I, it is present in much lower concentrations. It was first isolated from red blood cells by Warburg and Christian (157). The centrifuged cells are cytolyzed with water and after removal of the proteins with acetone, the coenzyme is precipitated as the barium salt. It is then dissolved in methanol–hydrochloric acid and precipitated with ethyl acetate. Coenzyme II may also be obtained from yeast by working up the mother liquor remaining after precipitation of cozymase as the cuprous salt. It has not been obtained in crystalline form and all preparations are readily soluble in water.

In contrast to enzyme I, this compound contains a third phosphoric acid residue. Warburg (156) proposed a partial structural formula for coenzyme II in 1936, and Euler and Schlenk (41) suggested the following formula on the basis of what was known about cozymase.



Since adenosinetriphosphoric acid has not been isolated as a breakdown product, the formula is not final. It is suggested that the third phosphoric acid group is linked to the adenylic acid part of the molecule in the same manner as is yeast adenylic acid. Since Adler and Elliot (7) have shown that coenzyme I can be converted to coenzyme II, it appears that the location of the phosphoric acid is the only question which has not been settled.

Table 1 shows that the stability of the two coenzymes is very similar.

TABLE 1

Stability of coenzymes I and II

FORM OF ENZYME	TREATMENT	COENZYME I	COENZYME II
Oxidised form	0.1 N HCl at 100°C.	50 per cent destroyed after 8 min. (42)	50 per cent destroyed after 7.3 min. (154)
	0.1 N NaOH	50 per cent destroyed after 17 min. (20°C.) (42)	50 per cent destroyed after 12 min. (23°C.) (154)
Reduced form	0.1 N HCl at 20°C.	Activity disappears (42) immediately (106)	Activity disappears immediately (157)
	0.1 N NaOH at 100°C.	Slight decrease after 10 min. (8)	
	0.1 N NaOH at 20°C.	Stable (8)	Stable (157)

While the two enzymes have similar properties and almost identical structures they show great specificity in their functions. In most cases a dehydrogenase which requires coenzyme I for activity cannot function in the presence of coenzyme II. A list of dehydrogenases requiring coenzyme I and coenzyme II is given by Schlenk (119).

5. Trigonelline: $C_7H_7NO_2$, *molecular weight 137; melting point, 215–218°C.*

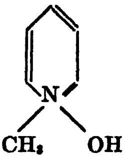
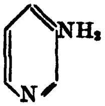
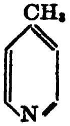
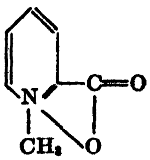
This compound was first isolated from plant material by Jahns (61) in 1885. In 1912 Ackermann (2) found that dogs given fairly large amounts of nicotinic acid excreted in the urine equal amounts of trigonelline and nicotinuric acid. It was isolated from starfish by Holtz, Kutscher, and Thielman (56) in 1924 and from liver extract by Subbarow and Dann (137).

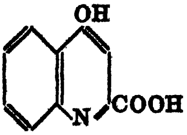
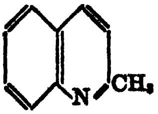
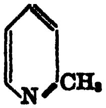
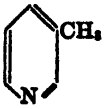
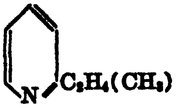
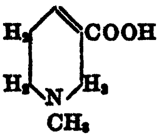
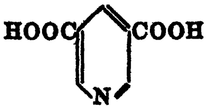
6. Nicotinuric acid (nicotinylglycine): $C_8H_8N_2O_3$, *melting point 240–242°C.*

This compound is a common constituent of urine but recent work by Sarett, Perlzweig, and Levy (117) indicates that in human urine the excretion of nicotinuric acid is very small in comparison to the amount of trigonelline. Nicotinuric acid is prepared by adding nicotinic acid chloride to a cold aqueous solution of glycine ethyl ester in slightly alkaline solution. The compound is crystallized from dilute hydrochloric acid solution. It is freely soluble in water and alcohol.

B. OTHER PYRIDINE COMPOUNDS FOUND IN NATURE

The following summary is taken from Bandier (16):

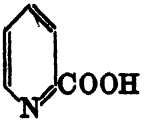
COMPOUND	ISOLATED FROM	FOUND BY
 Methylpyridinium hydroxide	Human urine	Kutscher and Lohmann (85) Ackermann and Kutscher (5) Ackermann *et al.* (3, 4)
 β-Aminopyridine	Liver extract	Subbarow, Dann, and Meilman (138)
 γ-Picoline	Horse urine	Achelis and Kutscher (1)
 Homarin	Lobster muscle; certain shell starfish	Hoppe-Seyler (57)

COMPOUND	ISOLATED FROM	FOUND BY
 Cynurenic acid	Dog urine	Liebig (89) and others
 α-Methylquinoline	Anal gland of the skunk	Aldrich and Jones (9)
 α-Picoline	Animal tar	Weidel (159)
 β-Picoline	Animal tar	Weidel (159)
 α-Methylethylpyridine	Animal tar	Weidel and Pick (161)
(C_7H_9N) Lutidine	Animal tar	Weidel and Herzig (160)
 Arecaidine	Naturally occurring alkaloid	Jahns (62)
 Dinicotinic acid	Liver extract	Subbarow (61)

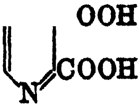
C. OTHER COMPOUNDS RELATED TO NICOTINIC ACID

Other compounds related to nicotinic acid are listed below:

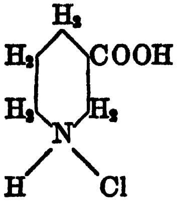
Isonicotinic acid
(m.p. 310–315°C.)



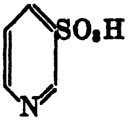
Picolinic acid
(m.p. 137°C.)



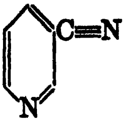
Quinolinic acid
(m.p. 190°C.)



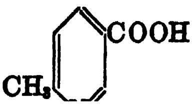
Nipecotic acid
hydrochloride
(m.p. 237–239°C.)



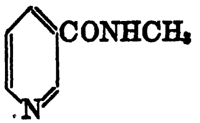
β-Pyridinesulfonic
acid (decomposes)



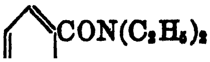
Nicotinonitrile
(m.p. 50°C.)



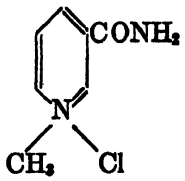
6-Methylnicotinic acid
(m.p. 206–207°C.)



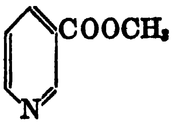
N-Methylnicotinamide
(m.p. 104–105°C.)



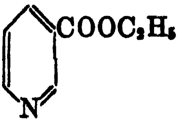
N,*N*-Diethylnicotinamide
(coramine)



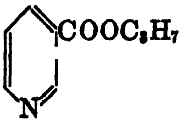
Nicotinamide methochloride
(m.p. 235°C.)



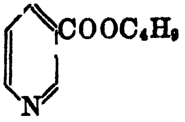
Methyl nicotinate



Ethyl nicotinate
(b.p. 86–88°C. at 5 mm.)



Propyl nicotinate
(b.p. 96–100°C. at 5 mm.)



Butyl nicotinate
(b.p. 111–117°C. at 5 mm.)

Since the activity of nicotinic acid was first demonstrated with the dog, it was natural that the studies on the biological activity of related compounds would be made on this animal. In 1938 Woolley, Strong, Madden, and Elvehjem (164) tested about twenty different compounds on a semiquantitative basis. It was evident immediately that a rather specific structure is required for anti-blacktongue activity. The α- and γ-isomers of nicotinic acid (picolinic acid and isonicotinic acid) were found to be inactive. Hexahydronicotinic acid (nipecotic acid) was also inactive. All the compounds tested in which one of the ring hydrogens had been substituted by a methyl or a carboxyl group or in which a methyl group had been added to the ring were inactive. The replacement of the carboxyl group by a sulfonic acid group or by a cyano group or the removal of the carboxyl entirely (pyridine) led in each case to inactive compounds. All these inactive compounds are listed in table 2, together with the organism on which tests have been made.

TABLE 2

Compounds which have shown no biological activity

COMPOUND	DOG	DYSENTERY BACILLI	*Staphylococcus aureus*	MAN	*Lactobacillus arabinosus*	*Proteus*
Pyridine	− (164)*					
β-Acetylpyridine hydrochloride	− (164)	− (28)				
6-Methylnicotinic acid	− (164)	− (28)				
Nipecotic acid	− (164)	− (28)				
Nicotinonitrile	− (164)	− (28)	− (70)			
Isonicotinic acid	− (164)	− (28)	− (70, 88)			
β-Pyridinesulfonic acid	− (164)	− (28)				
Picolinic acid	− (164)	− (28)	− (70, 88)	− (132, 148)		− (108)
Trigonelline	− (164)	− (28)	− (70, 88)	− (131, 132, 148)	− (130)	− (108)
β-Aminopyridine	− (136, 137, 164)	− (28)		− (131, 132, 148)		
Nicotinamide methochloride	− (164)				− (80)	

* Literature references are given in parentheses.

The studies with the dog indicated further that, in addition to nicotinic acid and its amide, only those compounds possess anti-blacktongue potency which are capable of oxidative or hydrolytic conversion to those substances in the body. Alkyl-substituted amides and the ethyl ester proved to be active. β-Picoline, which might be expected to be oxidized to nicotinic acid in the body, showed a fair degree of activity. Subbarow, Dann, and Meilman (138) reported that β-aminopyridine was highly active in the dog, but Strong, Madden, and Elvehjem (136) were unable to demonstrate any activity, and in a later note Subbarow and Dann (137) also reported the compound to be inactive. Later work has shown it to be inactive in man (132, 148) and in bacteria (28). Woolley, Strong, Madden, and Elvehjem (164) reported that nicotinuric acid was active, but recently Dann and Handler (23) have presented results which lead them to believe that nicotinuric acid is not a blacktongue preventative but may be able partially to replace nicotinic acid in the diet of the dog. Sarett (115) also found that dogs maintained on a low intake of nicotinic acid are unable to hydrolyze nicotinuric acid, but excrete it completely without metabolic change. Sarett, Huff, and Perlzweig (116) found almost 100 per cent of the nicotinuric acid in the urine of humans after intravenous injection of 100-mg. doses. Dorfman (28) found nicotinuric acid to be active for dysentery bacilli. If bacteria can hydrolyze nicotinuric acid, it should be active upon oral administration in animals; however, the positive results may have been due to impurities of free nicotinic acid.

Many of the compounds found active in the dog were soon tested on humans. Spies, Bean, and Stone (131) found nicotinic acid, nicotinamide and sodium nicotinate active, *N*,*N*-diethylnicotinamide (coramine) somewhat active, and trigonelline inactive. Spies, Grant, and Huff (132) found picolinic acid, α-picoline, and β-aminopyridine somewhat toxic, but obtained some improvement with β-picoline, 2,6-dimethylpyridine-3,5-dicarboxylic acid, and dinicotinic acid.

There seems to be some question about quinolinic acid. Woolley, Strong, Madden, and Elvehjem reported it to be inactive in the dog, but Vilter and Spies (145) concluded that it cured pellagra in humans. Dann, Kohn, and Handler (25) studied the action of quinolinic acid in dogs more carefully and found that complete protection was obtained only when this compound was given at a level one hundred times that needed when nicotinic acid was used. Waisman, Mickelson, McKibbin, and Elvehjem (153) found quinolinic acid inactive when injected into blacktongue dogs at a level ten times the effective dose of nicotinic acid. Dorfman, Koser, Reames, Swingle, and Saunders (28) found it weakly active for dysentery bacilli. In 1939 Bills, McDonald, and Spies (18) reported that pyrazinemonocarboxylic acid and 2,3-pyrazinedicarboxylic acid promptly cured the glossitis of pellagra in humans. However, Dann, Kohn, and Handler (25) and Waisman, Mickelson, McKibbin, and Elvehjem (153) were unable to demonstrate any appreciable activity of these compounds in dogs. Smith (128) has recently concluded that the only compounds in addition to nicotinic acid which justify their use on patients with pellagra are nicotinamide and coramine.

Briggs *et al.* (19) found that the growing chick requires a dietary source of nicotinic acid for optimal growth and for prevention of chick "blacktongue" when purified rations are used. The minimal level required was found to be approximately 1.8 mg. per 100 g. of ration. Only a few compounds have been tested on the chick, but the results with the nicotinic acid esters are most interesting. Ethyl nicotinate is only one-half as active as the free acid, while the propyl and butyl esters show correspondingly greater potency. Apparently the esters of the higher alcohols are more easily hydrolyzed in the digestive tract of chicks. The dog seems to be able to utilize the ethyl ester as readily as the free acid. A summary of the results with animals is given in table 3.

In a recent review on the B vitamin requirements of different microörganisms, Peterson (110) reports that molds and yeasts do not require nicotinic acid but that thirteen different species of bacteria are dependent upon a supply of this growth factor. Koser and Wright (79) have reported very recently that a yeast (*Torula cremoris*) needs nicotinamide or the acid for prompt and abundant growth. The most extensive studies have been made with the dysentery bacilli. Dorfman, Koser, Reames, Swingle, and Saunders (28) tested twenty-four diffour different compounds on three strains of *Shigella paradysenteriae*. In general the results agree very well with those obtained on animals. They found the methyl, ethyl, propyl, and butyl esters active; in fact, the methyl ester was more active than the free acid. The results were also very similar to those obtained by Knight (70) and Landy (88), who used *Staphylococcus aureus*. There was some discrepancy in the case of coramine, since Dorfman *et al.* found it to be active, while Knight and Landy reported no activity for this compound. Most of the bacteria used the amide more readily than the acid. Dorfman found the amide ten times as potent as the acid when the development of the organisms was compared 24 hr. after inoculation, while Knight found the amide five times more active for the staphylococci. Mueller (100), however, found the amide only one-tenth as effective as the acid for diphtheria bacilli. (See tables 3 and 4.)

While most organisms requiring nicotinic acid can use either the acid or the amide, the *Haemophilus parainfluenzae* is a well-known exception. Lwoff and Lwoff (90) had been working on a growth factor (V factor) for this organism, and in 1937 they (91) showed that the V factor could be replaced by either coenzyme I or coenzyme II.

The requirement of the influenza organisms for the preformed cozymase, the well-known function of the cozymase molecule in isolated enzyme systems, and the occurrence of cozymase in living material have led to the belief that nicotinic acid or its amide are merely building blocks for the coenzymes. Experimental evidence indicates that this may not be true for all organisms. One might explain Mueller's (100) finding that nicotinic acid is more potent than the amide in the nutrition of the diphtheria organism in either of two ways: (*1*) owing to a peculiarity in the converting mechanism, the acid might be more readily converted to cozymase than the amide; (*2*) the cells may be more permeable to the acid than to the amide. But the report by Dorfman, Stewart, Horwitt, Berkman, and Saunders (29) that nicotinamide is more potent than coenzyme I or coenzyme II in promoting growth of the dysentery organism is a little more difficult to explain. Apparently the amide is performing a function *per se* or being converted to a compound other than the coenzymes. However, differences in cell permeability may account for the different activities.

Schenk and Gingrich (124) have recently reported the nicotinamide-ribose nucleoside to be active for the influenza organism. This organism's synthetic power apparently falls down in the conversion of nicotinamide to the nucleoside. Koser, Berkman, and Dorfman (77) report that certain *Pasteurellae* are able to synthesize cozymase from nicotinamide but not from nicotinic acid, while *Bacterium coli* is an example of those organisms which can synthesize the entire coenzyme molecule. Fildes (44) has proved that *Proteus* is able to synthesize V factor from nicotinic acid, and we are perhaps safe in assuming that other organisms which grow on nicotinic acid are able to synthesize the coenzymes, if nicotinic acid is furnished.

Thus, it is evident that organisms vary greatly in their ability to synthesize the coenzymes and it appears that in the case of some organisms at least, cozymase may not be the most active compound.

TABLE 3

Comparative biological activity of nicotinic acid and related compounds

COMPOUND	MAN	DOG	CHICK (19)	DYSENTERY BACILLI (28)	*Staphylococcus aureus*	*Lactobacillus arabinosus*	*Proteus* (108)
Nicotinic acid.......	+++	+++	+++	+++	++	+++	+
Nicotinamide........	+++ (131)*	+++ (164)		+++++	++++ (70, 88)	+++ (80, 130, 142)	+
Methyl nicotinate....				++++	+++ (70)		
Ethyl nicotinate.....		++ (164)	+	++	++ (88)	− (80)	+
Propyl nicotinate....			+	+		− (80)	
Butyl nicotinate.....			++			+ (80)	
Quinolinic acid	+ (145) − (25)	− (25, 153, 164)		+ (low)	− (88)		
β-Picoline	+ (132, 148)	+ (164)		−	− (70)		
Nicotinuric acid		+ (164) − (23)		+++	++ (88)	+++ (130)	+
N-Methylnicotinamide..............		++ (164)		++			
N,*N*-Diethylnicotinamide..............	++ (131)	++ (129, 164)		+	− (70, 88)		+

* Literature references are given in parentheses.

Studies involving sulfa drugs have been made both to obtain some clue to the mode of action of the drugs and to get a better understanding of nicotinic acid metabolism. McIlwain (94) has studied the bacteriostatic effects of sulfonic acid derivatives of nicotinic acid on *Staphylococcus aureus* and their counteraction by nicotinic acid, nicotinamide, and cozymase, and has found a definite competitive effect. West and Coburn (162) found that cozymase, but not nicotinic acid, reversed the bacteriostatic effect of sulfapyridine on this same organism. Straus, Dingle, and Finland (134) were unable to confirm these results, but Spink, Vivino, and Mickelson (133) report cozymase to have counteracting effects under certain conditions. Two recent reports strengthen the belief that sulfapyridine interferes with nicotinamide–enzyme systems. Dorfman and Koser (27) have found that nicotinamide or cozymase reverses the depression of respiration in the dysentery organism caused by sulfapyridine. *p*-Aminobenzoic acid is unable to reverse this effect. Furthermore, the addition of nicotinamide to the medium decreases the amount of *p*-aminobenzoic acid necessary for counteraction of bacteriostatic effects. Teply, Axelrod and Elvehjem (143) have found nicotinamide, nicotinamide-ribose nucleoside, and cozymase to have almost equal activity in partially counteracting the bacteriostatic effect of sulfapyridine on *L. arabinosus*. Nicotinic acid was of such low potency that its effect might well be due to contamination with the highly active *p*-aminobenzoic acid. Further work involving more drugs and more organisms is necessary to clarify the picture, but there is little doubt that sulfa drugs can interfere with nicotinic acid metabolism.

TABLE 4

Comparative activity of nicotinic acid, nicotinamide, nicotinamide-ribose nucleoside, and cozymase

ORGANISM	NICOTINIC ACID	NICOTINAMIDE	NICOTINAMIDE-RIBOSE NUCLEOSIDE	COZYMASE
Bacterial growth promotion				
Influenza organism (124)	−	−	+	++
Pasteurellae (77)	−	+		+
Dysentery bacilli* (28, 29)	+	++		+
Staphylococcus aureus† (88, 100, 133)	+	++		++
Proteus (44)	+	+		+
Lactobacillus arabinosus (142)	+	+	+	+
Diphtheria organism (100)	++	+		
Sulfapyridine counteraction				
Staphylococcus aureus (growth) (133, 162)	−			+
Lactobacillus arabinosus (growth) (143)	−‡	+	+	+
Dysentery bacilli (respiration) (27)		+		+

* No direct comparison of nicotinic acid and cozymase is reported.

† No direct comparison of nicotinamide and cozymase is reported.

‡ Slight activity found was probably due to contamination with *p*-aminobenzoic acid.

The data summarized so far are important from a qualitative point of view, but in order to use these compounds successfully in nutrition and to understand the related metabolic processes more accurate quantitative methods must be used. Available methods for measuring the nicotinic acid content of natural materials include biological, physical, chemical, and microbiological procedures.

In the early studies the dog was the only animal that could be used for extensive assays. At first a modified Goldberger diet was used (153) but more recently synthetic diets have been employed (118). In either case, the method is expensive and requires considerable time because a standard response must be established with pure nicotinic acid before the material to be assayed can be fed. The dog assay cannot be used for foods very low in the vitamin because sufficient food to give a typical response cannot be fed at one time; however, it still provides a means of checking the simpler methods. Liver seems to show a higher potency by the animal assay than by any of the other methods, a fact which may be due to the presence of so many other growth factors in liver. The chick has recently been used with considerable success in the assay of certain foods (19). The hamster has been suggested as a useful assay animal (113), but recent work indicates that this animal does not need nicotinic acid preformed in the diet (21). Biological assays measure total nicotinic acid activity and, as shown in table 3, different species may utilize different nicotinic acid derivatives with varying efficiency. It is thus difficult to decide which animal will give the best results in terms of human nutrition. It is unfortunate that so little quantitative work has been done with the monkey.

Methods involving the growth response of moth larvae (114), isolated tobacco roots (26), and pea roots (6) have been found to be of no practical value.

Spectrographic determination of nicotinic acid has been used by Holiday (55), and Karrer and Benz (64) developed a spectrophotometric procedure for nicotinamide.

Colorimetric methods for the estimation of nicotinic acid have been intensively investigated during the past six years. In 1899 Vongerichten (151) found that the addition of 2,4-dinitrochlorobenzene and alkali to pyridine produces a yellow color. Karrer and Keller (65) showed that nicotinic acid and the amide gave a similar reaction. Vilter, Spies, and Mathews (150) studied the reaction with a number of related compounds and concluded that pyridine, nicotinic acid, nicotinamide, *N*, *N*-diethylnicotinamide, α-picoline, and nicotine gave a color reaction, while trigonelline and picolinic acid yielded no color.

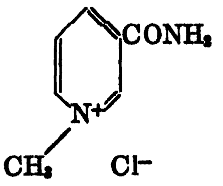
König (73) in 1904 showed that pyridine reacts with cyanogen bromide and a primary or secondary amine to give a color varying from yellow to violet. This reaction has been used most extensively for the chemical estimation of nicotinic acid and related compounds but a variety of amines have been used in the conjugation. Several workers (82, 95, 107, 127, 140) have used aniline. Bandier and Hald (17) found most consistent results with *p*-methylaminophenol and Harris and Raymond (53), Kodicek (71), and Arnold, Schreffler and Lipsius (11) based their procedures on the use of *p*-aminoacetophenone. Studies on the details of the reaction have been reviewed by Waisman and Elvehjem (152) and by Bandier (16). Bandier also includes extensive studies on the specificity of the color reaction. He found, using *p*-methylaminophenol, that pyridine yielded a yellow color which in equimolar amounts was more intense than the color with nicotinic acid. In the presence of potassium dihydrogen phosphate the color with pyridine was much less. Fortunately there is very little, if any, pyridine in most biological materials. Pyridine derivatives which are substituted in the α- or γ-position do not give a color reaction. This fact probably explains why vitamin B_6 or pyridoxine gives no reaction. Kuhn and Löw (83) and Kringstad and Naess (82) had found that vitamin B_6 gave no color with cyanogen bromide and aniline. Pyridinium compounds also failed to give a color, and since the nitrogen atom in the coenzymes is pentavalent they do not show any activity until hydrolyzed. For equimolar quantities of pyridine derivatives substituted in the β-position the intensity of the color varied as follows: nicotinic acid 100, nicotinamide 142, nicotinuric acid 42, β-aminopyridine 15, nicotine 8, and *N*, *N*-diethylnicotinamide 6. β-Picoline yielded a very pale color. From these results it would appear that relatively little difficulty would be encountered from interfering substances in biological material except in the case of blood and urine from smokers.

The chemical procedure did give rather consistent results for animal tissues: for example, the following values were obtained for beef muscle in four different laboratories: Bandier (15) 4.9, Kringstad and Naess (82) 4.9, Kodicek (71) 4.3, and Waisman and Elvehjem (152) 4.8. The occurrence of interfering colors in natural materials such as bile pigments, riboflavin, carotenoids, etc., has proved a definite handicap in reading the color which is developed. Therefore, it is necessary either to remove the nicotinic acid from the pigments or to remove the pigments from the nicotinic acid before the color development. Melnick and Field (95) attempted to adsorb the pigments in an acid alcohol solution with a special charcoal. Dann and Handler (24) maintain that it is essential to remove all, or virtually all, of the color from the extract and have used Lloyd's reagent and lead hydroxide. They also showed that charcoal removes only part of the color and in addition removes nicotinic acid from the acid alcohol solution.

The chemical method has been used by several workers for the estimation of nicotinic acid in blood. Pearson (107) found the method described by Swaminathan (140) the most satisfactory for blood. Klein, Perlzweig, and Handler (68) have discussed the various methods proposed for blood and have outlined a procedure for the analysis of the blood cells and the plasma.

The estimation of nicotinic acid and related compounds in urine is important in order to carry out balance studies, but this determination is difficult not only because of the presence of interfering substances but because much of the ingested nicotinic acid is excreted as trigonelline. Rosenblum and Jolliffe (112) found the method of Bandier and Hald to be a simple and specific procedure for the estimation of nicotinic acid and amide in urine. More recent work has taken into account the presence of nicotinuric acid and trigonelline, and improved methods have been described by Melnick, Robinson, and Field (98) and by Perlzweig, Levy, and Sarett (109). The free nicotinic acid, the amide, and nicotinuric acid are determined after acid hydrolysis. This treatment does not affect the trigonelline, which is determined after alkaline hydrolysis. Measurements on trigonelline excretion are complicated by the fact that the compound is present in appreciable amounts in coffee and legumes and finds its way into the urine as well as that formed from ingested nicotinic acid. Sarett, Huff, and

Perlzweig (116) found the normal daily excretion of acid-hydrolyzable nicotinic acid derivatives in normal humans to be 0.7 to 2.2 mg. The daily excretion of trigonelline when the subjects were on a controlled diet was 9 to 13 mg. When high amounts of nicotinic acid are ingested, all of the vitamin cannot be accounted for in the urine. In this connection it is interesting to refer to the work of Najjar and Wood (104). They found in human urine a small amount of a substance soluble in butyl alcohol which gave a bluish fluorescence with ultraviolet light (substance F_2). When a dose of 50 mg. of nicotinic acid was given, an increased amount of the substance was excreted. An increase in the urine could be detected within an hour and persisted for 4 to 6 hr. They compared the fluorescence of the compound with that of twenty-seven different pyridine derivatives but concluded that none of the compounds tested could be identified with the unknown compound. Huff and Perlzweig (60) have recently concluded that F_2 appears to be *N*-methylnicotinamide or a labile precursor which yields the compound in the course of isolation.



Najjar, Scott, and Holt (103) have commented on this conclusion as follows: F_2 appears to be a pyridine compound. The original compound does not give a cyanogen bromide reaction but after alkaline hydrolysis a positive cyanogen bromide test is obtained. It is biologically active. Results indicate that one of the *N*-methyldihydronicotinamides is indistinguishable from F_2 by its adsorption properties, solubility in eleven organic solvents, and its reactions with alkali, potassium ferricyanide, nitrous acid, acetone, and sulfanilic acid. They do not feel justified in identifying F_2 as an *N*-methyldihydronicotinamide for three reasons: (*1*) because one of the *N*-ethyl isomers likewise possesses these identical properties; (*2*) because acetylation of F_2 and of *N*-methyl- and *N*-ethyldihydronicotinamides gives compounds with different fluorescent properties and solubilities; and (*3*) because the absorption of F_2 shows characteristic differences. It is obvious that we need to know more about these compounds before completely quantitative measurements can be made on urine.

Noll and Jensen (105) have discussed some of the difficulties encountered in applying the chemical methods to milk and milk products.

When the cyanogen bromide method was applied to plant materials (71, 152), values for nicotinic acid were obtained which were not reconcilable with the known fact that many cereals are low in the anti-pellagra factor. The direct extraction of cereals with alkali or acid results in the extraction of chromogens which give an exceptionally high final value. Kodicek (71), Waisman and Elvehjem (152), and Melnick, Oser, and Siegel (97) have obtained values more in accord with accepted nicotinic acid potency when an aqueous extract is made first and then treated with acid or alkali. Hale, Davis, and Baldwin (49) have used the chemical procedure on a large variety of plant products and have compared the results with those obtained by microbiological assay. They conclude that plant materials may be divided into two classes on the basis of their response to various extraction and hydrolytic treatments. Alkaline hydrolysis of an aqueous extract gives the most satisfactory results for the non-chlorophyll-containing seed and roots, while acid hydrolysis of the chlorophyll-containing part of the plant gives the lowest and most accepted values. In general, there was excellent agreement between the chemical and microbiological results except in the case of certain forage material. They suggest that the chemical method must be used with caution, if at all, for the forage part of the plant.

It is also interesting to point out that Lamb (87) and Melnick and Oser (96) have used the chemical method for the quantitative estimation of nicotinic acid and nicotinamide when they occur together. This method is applicable largely to vitamin mixtures. When cyanogen bromide and aniline are used, the relationship between the maximum extinction coefficients and the time for their development is characteristic for the acid and the amide.

A number of microbiological methods have been proposed for the estimation of nicotinic acid. In 1938, Lwoff and Querido (92) described the use of *Proteus* and, in the same year, Fraser, Topping, and Sebrell (45) developed an assay based on *Shigella paradysenteriae* (Sonne) and Koser, Dorfman, and Saunders (78) used the dysentery bacillus. However, it was not until 1941 that a satisfactory procedure for assaying all types of materials was developed. Snell and Wright (130) used *L. arabinosus* as the test organism and developed a medium which has been highly successful. Krehl, Strong, and Elvehjem (81) have recently made slight modifications in the procedure. A great variety of biological materials have been analyzed by this method and at present there is no reason to doubt the accuracy of any of the results.

Best results are probably obtained with food materials if all the nicotinic acid-containing compounds are hydrolyzed to the free acid before the bacterial assay is carried out. However, the nicotinamide, the nucleoside, and coenzyme I all give equivalent activity with *L. arabinosus*. There may be some question about nicotinuric acid. Snell and Wright (130) concluded that it was active, but since it apparently is difficult to prepare nicotinuric acid free from nicotinic acid a final decision may have to be made later. Certain natural materials contain a compound which shows no activity in the *L. arabinosus* assay until it is hydrolyzed. Andrews, Boyd, and Gortner (10), working with cereals and cereal products, found that water and dilute acid extraction gave lower values for nicotinic acid than stronger acids and alkali. They concluded that this discrepancy could be attributed either to the formation of growth-stimulating substances or to the liberation of active nicotinic acid compounds by hydrolysis of a less active or inactive precursor. Evidence was presented which indicated that the second possibility was the correct explanation. Cheldelin and Williams (20) also found that acid or alkaline extraction of cereals gave higher values than enzymatic digestion alone. The increase in both the acid and alkaline extractions was attributed to substances convertible to nicotinic acid, and it was suggested that trigonelline might be responsible for part of the increase in the alkaline treatment. They concluded that the substance formed by hydrolysis was actually nicotinic acid because of the similar results with both microbiological and chemical methods. Extensive work in the authors' laboratory also strongly suggests that the precursor not only yields nicotinic acid but that it is biologically active at least in the dog before hydrolysis.

One would expect that the quantitative estimation of coenzymes I and II would be more difficult because the molecular structure is more complicated and the molecule itself is easily disrupted. In spite of these difficulties, some rather accurate determinations have been made. Again, biological, physical, chemical, and microbiological methods have been used.

Harden (52) measured cozymase activity by using a press extract of yeast as a source of the enzyme systems and a boiled yeast extract as a source of the coenzyme. The method of the determination of coenzyme I as developed by Euler (32) and Myrbäck (101) is based on the principle that the addition of varying amounts of the coenzyme to a washed yeast preparation will produce rates of fermentation which are proportional, within certain limits, to the amount of coenzyme I added. The use of this yeast fermentation method has been described in detail by Axelrod and Elvehjem (12). Schlenk and Vowles (125) have also described improvements in the yeast fermentation method. Jandorf, Klemperer, and Hastings (63) have made use of the activity of coenzyme I in a glycolysis system rather than in fermentation. The amount of phosphoglyceric acid produced in a given time in the presence of bicarbonate buffer is measured monometrically in a Warburg apparatus. Very few measurements have been made in the case of coenzyme II, but the original system described by Warburg (157) may be used. If the coenzyme is the limiting factor in this system, the rate of oxygen uptake is a measure of its concentration.

Physical methods depend upon the spectrophotometric determination of the corresponding dihydro compounds. In this case the solutions containing the coenzymes must be free from impurities that absorb in the ultraviolet region in which the dihydro coenzymes exhibit their characteristic absorption. The details of these methods have been summarized by Hogness and Potter (54). This procedure has been used mostly in studies on the related enzyme systems rather than in studies on the distribution of the coenzymes in tissues.

A chemical estimation of the two pyridine nucleotides may be made by determining the amount of nicotinamide present in a tissue before and after hydrolysis. The increase in the amount of the amide can then be used to calculate the amount of coenzyme originally present. Euler and coworkers (43) used this method in their early studies on the distribution of coenzymes in dog and rat tissues.

The microbiological methods are based on the fact that *Hemophilus influenzae* and *Hemophilus parainfluenzae* require the preformed coenzymes.

In 1938 Kohn (74) developed the so called V factor technique for the estimation of total coenzyme I and II, using *H. parainfluenzae* as the test organism. Vilter, Vilter, and Spies (146) developed a method very similar in nature but used *H. influenzae* as the organism. Further details of this method have been published by Vilter, Koch, and Spies (149). It is important to remember that these methods do not distinguish between the two coenzymes and also that Schlenk and Gingrich (124) have shown that the nicotinamide nucleoside is also measured if present.

Regardless of how the actual estimations are made, two difficulties are always encountered which affect the accuracy of the final values. Since cozymase has not been obtained in absolutely pure form, it is difficult to secure a standard for use in the various methods. Some of the values in the literature are probably high because the standard cozymase used had an activity considerably below 100 per cent. Recent studies by Handler and Dann (50) indicate that some of the preparations that have been used have a maximum absolute purity of 76 per cent.

The other problem involves the prevention of destruction of the coenzyme during the preparation of the sample for analysis. Euler and coworkers (35, 36, 40) observed very early that the coenzyme content of tissues decreases very rapidly after the death of the animal, especially when the cell structure is destroyed. Mann and Quastel (93) found that brain suspensions rapidly destroyed cozymase and suggested the presence of a nucleotidase. Liver and kidney were less active and skeletal and heart muscles contained little if any of the enzyme. They found that nicotinamide reduced the rate of destruction and postulated that the nicotinamide and cozymase compete for the active center of the nucleotidase. Handler and Klein (51) have studied the inactivation of the pyridine nucleotides by a number of different animal tissues and found that in each case nicotinamide is liberated from the rest of the molecule. Nicotinamide was found to be quite specific in preventing the decomposition. In quantitative methods, this destruction can be prevented by freezing the tissues as soon as they are removed from the animal (12).

In spite of the difficulties which have been discussed, rather definite values are available for the distribution of cozymase in a variety of biological materials. The cozymase content of liver falls between 400 and 800 γ per gram of fresh tissue. The amount probably varies with the level of nicotinic acid in the ration. Briggs *et al.* (19) found much more cozymase in the breast muscle of chicks when the diet contained 10 mg. per 100 g. than when the amount in the diet was less than 2 mg. per 100 g. but adequate to give normal growth. Axelrod and Elvehjem (13), as well as Kohn, Klein, and Dann (76), have shown a decrease in the cozymase content of liver and muscle, but little change in the brain or kidney during nicotinic acid deficiency in dogs and pigs. A definite decrease was found in the muscle from human cases of pellagra (14). The coenzyme concentration in the red blood cells of pellagrous and normal individuals has been studied by Kohn (75, 76), Spies (147) and Elvehjem (14). All agree that the coenzyme content may be increased by ingestion of nicotinic acid and that the decrease during nicotinic acid deficiency is only slight. It has been concluded that there is no diagnostic value to be obtained from determinations of coenzyme I in borderline cases of deficiency diseases.

Pitman and Fraser (111) measured the coenzyme (V factor) content of urine from normal and deficient dogs but found no difference in the amount excreted.

The evolution of our knowledge of the biochemistry of nicotinic acid has followed much the same course as that for other biologically active substances. When the importance of nicotinic acid was first recognized the picture appeared to be very simple: namely, all living tissues contain coenzymes I and II and nicotinic acid is needed for the construction of these molecules. Certain species can manufacture the nicotinic acid needed for these compounds, while others must rely upon an outside source. In the case of humans, nicotinic acid must be supplied preformed in the diet and the syndrome resulting from an inadequate intake has come to be known as pellagra. As the studies continue it is still evident that living cells require highly specific structures but these structures are found in a variety of natural compounds, some of which are biologically active and others inactive. All these related compounds must be considered, whether we are measuring dietary intake, metabolism, or excretion, and the complete picture cannot be finished until they have been recognized and methods for their quantitative estimation established.

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THE HYDROXAMIC ACIDS

HARRY L. YALE
Shell Development Company, Emeryville, California

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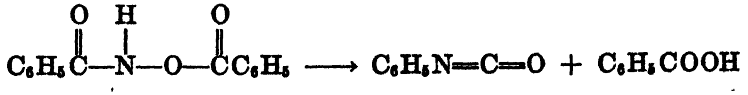
CONTENTS

I. The hydroxamic acids 209
  A. Foreword 209
  B. Nomenclature 210
  C. Structure 212
  D. Monohydroxamic acids 224
  E. Derivatives of monohydroxamic acids 231
    1. Alkyl- and aryl-substituted monohydroxamic acids 231
    2. Monohydroxamyl halides 235
    3. Carbamylhydroxamic acids 237
    4. Thiohydroxamic acids 238
    5. Arylsulfonhydroxamic acids 239
  F. Dihydroxamic acids 240
    1. Alkyl- and aryl-substituted dihydroxamic acids 240
  G. Metal salts of the mono- and di-hydroxamic acids 241
  H. Triacylated hydroxylamine compounds 242
II. The Lossen rearrangement 242
  A. Mechanism of the Lossen rearrangement 243
  B. Anomalous behavior in the Lossen rearrangement 247
  C. Temperature and alkalinity as factors in the Lossen rearrangement 249

I. THE HYDROXAMIC ACIDS

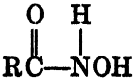
A. FOREWORD

In a paper which appeared in 1869, H. Lossen (167) reported that the reaction between diethyl oxalate and hydroxylamine yielded an acidic compound which he named oxalohydroxamic acid. Later, W. Lossen (169) found that benzoyl chloride and hydroxylammonium chloride gave a mixture of benzohydroxamic acid, benzoyl benzohydroxamate, and dibenzoyl benzohydroxamate. He observed that benzoyl benzohydroxamate when heated above its melting point liberated a lachrymatory substance (phenyl isocyanate), and in this fashion he discovered the reaction now known as the Lossen rearrangement.



$$C_6H_5\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-O-\overset{\overset{O}{\|}}{C}C_6H_5 \longrightarrow C_6H_5N{=}C{=}O + C_6H_5COOH \qquad (1)$$

The structure of the hydroxamic acids was first brought to the attention of W. Lossen (170) by the observation that the product obtained by the interaction of anisohydroxamic acid and benzoyl chloride was different from the product obtained with benzohydroxamic acid and anisoyl chloride. He introduced the term "metamers" to describe these compounds, erroneously believing that both acyl groups in each compound were attached to the nitrogen atom of the hydroxylamine molecule. Later (173), he realized that in the successive acylation of hydroxylamine each of the hydrogens of the hydroxylamine molecule behaved differently from the other two, and as a result of this, proposed the "hydroxyoxime" structure, $RC(OH){=}NOH$, as the correct one. Such a structure served to explain the difference between ethyl benzohydroxamic acid, $C_6H_5C(OC_2H_5){=}NOH$, and ethyl benzohydroxamate, $C_6H_5C(OH){=}NOC_2H_5$, as well as the hydrolytic products obtained with a variety of acylated and alkylated monohydroxamic acids. He considered the α-, β-, and γ-forms of dibenzoyl benzohydroxamate or the α- and β-forms of ethyl benzohydroxamic acid in each instance as physically different manifestations of the same parent compound. It was at this time that he became considerably involved in a controversy on structure with Werner, Tiemann, and others. Werner (305, 306, 309) presented evidence which indicated that the α- and β-forms of ethyl benzohydroxamic acid were geometric isomers. Tiemann preferred the "hydroxyamide" structure:



$$R\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}OH$$

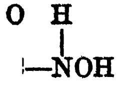
Various attempts to prepare compounds of the hydroxyoxime structure demonstrated their instability under conditions known to have little effect on the hydroxamic acids.

To the controversy on the structure of the hydroxamic acids can be attributed the development of Angeli's "nitrosyl" theory. In an effort to establish the structure of these compounds Angeli (1), searching for a new method for their synthesis, succeeded in preparing sodium nitrohydroxamate, $Na_2N_2O_3$. Under certain conditions, this latter compound served as a source of free nitrosyl, NOH.

W. Lossen neglected the development of the rearrangement which bears his name, either as a consequence of his complete occupation with the structure of the hydroxamic acids, or from a lack of interest. He was aware of its similarity to the Hofmann rearrangement (175). Tiemann (290) first suggested the existence of a transitory univalent nitrogen derivative as an intermediate in the rearrangement. This view was enlarged by Stieglitz (280–283) and by Jones (133, 134, 136, 137, 140, 142–148). Jones and his students were concerned also with the effects on the rearrangement of introducing into the molecule certain groups capable of existing as free radicals. The existence of such free radicals was critically studied by Wallis and Moyer (302) and Bell (49). Hauser and his students (57, 105, 247) showed that the velocity of rearrangement with the dihydroxamic acids, RCONHOCOR′, was directly related to the ionization constant of the organic acid (R′COOH) eliminated, if R was kept constant, or indirectly related to the ionization constant of the carboxylic acid RCOOH, if R′ was held the same.

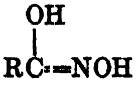
B. NOMENCLATURE

The nomenclature of the hydroxamic acids, particularly in the early literature, had an ambiguity which stemmed directly from the uncertainty regarding their structure. In this review, it is assumed that the tautomers (I and II) of the monohydroxamic acids are capable of existence.



$\overset{O}{\|}\text{—}\overset{\overset{H}{|}}{N}OH$

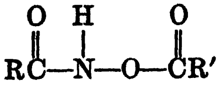
I



$R\overset{\overset{OH}{|}}{C}{=}NOH$

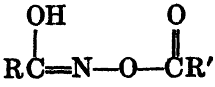
II

When a monohydroxamic acid is acylated, the first acyl group which enters is attached to oxygen, and is present as shown in the tautomeric forms III and IV; the second acyl group which enters gives rise to two isomeric compounds, V and VI.



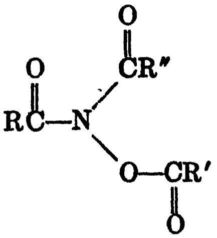
$R\overset{\overset{O}{\|}}{C}—\overset{\overset{H}{|}}{N}—O—\overset{\overset{O}{\|}}{C}R'$

III

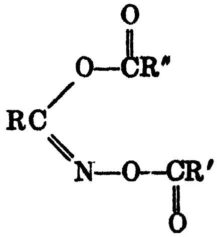


$R\overset{\overset{OH}{|}}{C}{=}N—O—\overset{\overset{O}{\|}}{C}R'$

IV



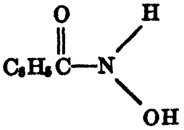
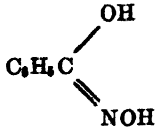
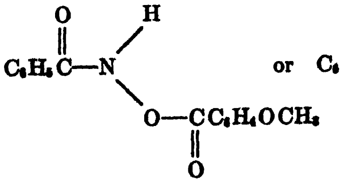
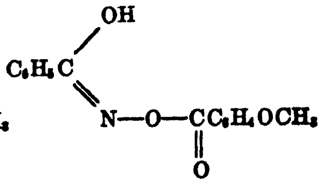
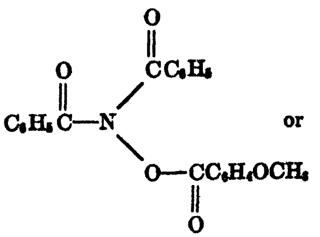
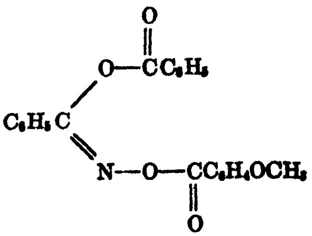
V

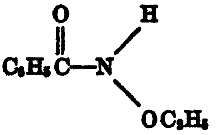
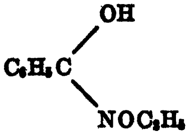
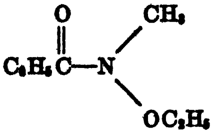
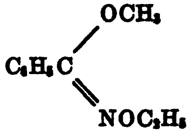
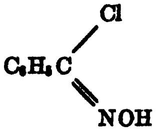
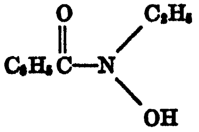
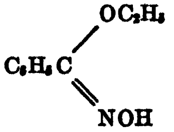


VI

When a monohydroxamic acid is alkylated, the order of alkylation and the products possible are similar to those encountered in acylation.

The following are examples of the system of nomenclature used for the hydroxamic acids and their derivatives:

NAME	FORMULA
Benzohydroxamic acid	 or 
Anisoyl benzohydroxamate	 or 
Benzoyl anisoyl benzohydroxamate	 or 

NAME	FORMULA
Ethyl benzohydroxamate....	 or 
Methyl ethyl benzohydroxamate....	 or 
Benzohydroxamyl chloride..............	
Ethyl benzohydroxamic acid*.................	 or 

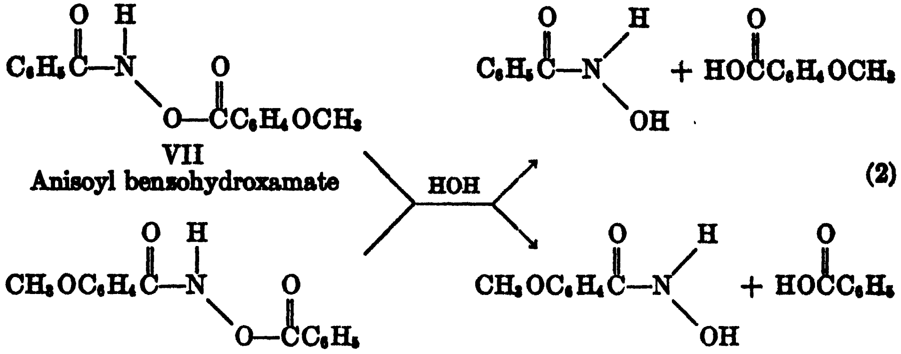
* This compound has been named arbitrarily to differentiate it from its isomer, ethyl benzohydroxamate. It should be noted that the reaction between an *N*-alkyl(or aryl) hydroxylamine, R'NHOH, and an acyl halide yielded a product of the general formula R'N(OH)COR. This type of compound when so prepared possesses one structure and is named systematically as a member of this group.

For conciseness, wherever two structural formulas are possible, but where either will serve to illustrate, only one formula will be indicated.

C. STRUCTURE

When an acyl group replaces one of the nitrogen-bound hydrogens in the hydroxylamine molecule, a monohydroxamic acid, RCONHOH, is formed. In their capacity to undergo alkylation as well as in their ability to form colored metallic chelates, the monohydroxamic acids strongly resemble compounds known to exist in tautomeric equilibria. A considerable amount of evidence is at hand to substantiate the existence of the tautomeric form of the monohydroxamic acid, RC(OH)═NOH. With two exceptions (22, 91, 92, 148, 232) it has not been possible to separate these two forms. Reactions of monohydroxamic acids can be attributed to either structure. The probable existence of these tautomers has made more complex the structure of the progressively acylated or alkylated monohydroxamic acids.

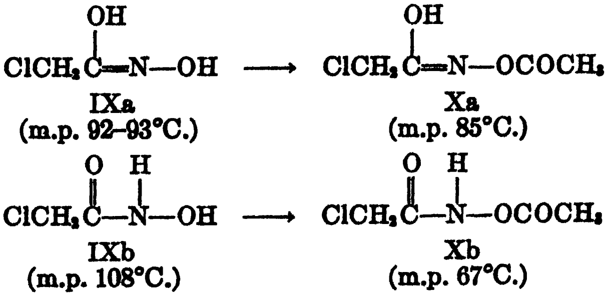
In the very early work (72, 170) an uncertainty existed as to which hydrogens in the hydroxylamine molecule were substituted by the first and second acylating groups. It is now generally accepted that the first acyl group is bound to the nitrogen atom, while the second acyl group is held by the oxygen. As a result, anisoyl benzohydroxamate (VII) prepared from anisoyl chloride and benzohydroxamic acid is isomeric with benzoyl anisohydroxamate (VIII) prepared from benzoyl chloride and anisohydroxamic acid. When subjected to hydrolysis, these compounds yielded different products (171).


VII
Anisoyl benzohydroxamate

(2)
VIII
Benzoyl anisohydroxamate

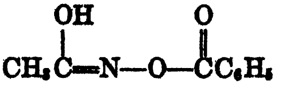
From these hydrolytic reactions, it was evident that the second acyl group, attached to oxygen, was held less firmly than the first, which was attached to nitrogen. From studies on the hydrolysis of the triacylated hydroxylamines, it was shown that the third acyl group cleaved most readily. This was paradoxical, in view of the extreme difficulty with which the third acyl group was introduced (124). It appeared reasonable to assume that the hydrolysis, as well as the acylation, was not affected by steric relationships within the molecule.

Evidence for the existence of tautomers of the structures I and II was presented by Jones and Werner (148), who prepared chloroacetohydroxamic acid and found that the melting point, originally 92–93°C. (IXa), was raised to 108°C. (IXb) after several days. Both forms gave identical analyses. The acetyl derivatives melted at 85°C. (Xa) and 67°C. (Xb), respectively. In some earlier work,


$$\mathrm{ClCH_2\overset{OH}{\overset{|}{C}}{=}N{-}OH} \longrightarrow \mathrm{ClCH_2\overset{OH}{\overset{|}{C}}{=}N{-}OCOCH_3}$$
IXa (m.p. 92–93°C.) Xa (m.p. 85°C.)

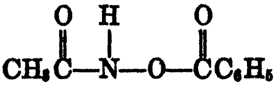
$$\mathrm{ClCH_2\overset{O}{\overset{\|}{C}}{-}\overset{H}{\overset{|}{N}}{-}OH} \longrightarrow \mathrm{ClCH_2\overset{O}{\overset{\|}{C}}{-}\overset{H}{\overset{|}{N}}{-}OCOCH_3}$$
IXb (m.p. 108°C.) Xb (m.p. 67°C.)

Jones (132) obtained two forms of benzoyl acetohydroxamate, which were separated by means of their different solubilities in ether. On standing, the product possessing the lower melting point (69–70°C.) became opaque and after several weeks was transformed into a product identical with the higher melting form (98–99°C.). Jones believed that the latter compound corresponded to the structure XIb, while the metastable form was represented by XIa.



$\mathrm{CH_3\overset{\overset{OH}{|}}{C}{=}N{-}O{-}\overset{\overset{O}{\|}}{C}C_6H_5}$

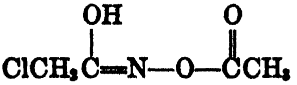
XIa



$\mathrm{CH_3\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}O{-}\overset{\overset{O}{\|}}{C}C_6H_5}$

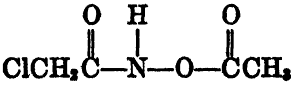
XIb

On this basis, Xa and Xb could be represented as shown below:



$\mathrm{ClCH_2\overset{\overset{OH}{|}}{C}{=}N{-}O{-}\overset{\overset{O}{\|}}{C}CH_3}$

Xb

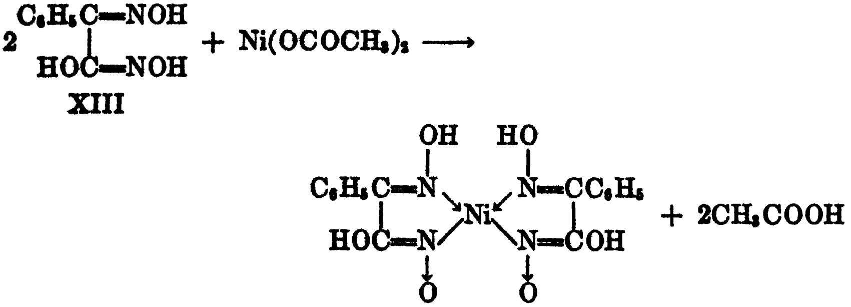


$\mathrm{ClCH_2\overset{\overset{O}{\|}}{C}{-}\overset{\overset{H}{|}}{N}{-}O{-}\overset{\overset{O}{\|}}{C}CH_3}$

Xa

It will be remembered that Xb was derived from the stable form of chloroacetohydroxamic acid (IXb). Many cases have been reported where the enolic form of two tautomeric compounds possessed the lower melting point. An inconsistency can be noted here when this observation is extended from the tautomeric forms I and II to the tautomeric forms III and IV.

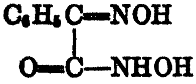
Gastaldi (91, 92) obtained two forms of benzoylformohydroxamic acid, $\mathrm{C_6H_5COCONHOH}$. The α-form was obtained by the reaction between ethyl phenylglyoxylate and hydroxylamine; the β-form was obtained by isomerizing the α-form with dilute acetic acid. The two modifications were differentiated by their behavior toward acetic anhydride, sodium hydroxide, sodium ethoxide, and *o*-phenylenediamine. Baiardo (22) found that the oxime of the α-form (XII) when treated with nickel acetate gave no precipitate or change in color, while the oxime of the β-form (XIII) gave a red colored precipitate. Presumably, the latter modification possessed a structure capable of forming a chelate with nickel,



$$2\begin{array}{l}\mathrm{C_6H_5C{=}NOH}\\ \quad|\\ \mathrm{HOC{=}NOH}\end{array} + \mathrm{Ni(OCOCH_3)_2} \longrightarrow \begin{array}{c}\mathrm{OH\quad HO}\\ \mathrm{C_6H_5C{=}N\searrow\ \swarrow N{=}CC_6H_5}\\ \mathrm{|\qquad Ni \qquad |}\\ \mathrm{HOC{=}N\nearrow\ \nwarrow N{=}COH}\\ \mathrm{\downarrow\qquad\quad\downarrow}\\ \mathrm{O\qquad\quad O}\end{array} + \mathrm{2CH_3COOH} \quad (3)$$

XIII

while the former,

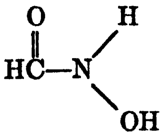


$\begin{array}{l}\mathrm{C_6H_5C{=}NOH}\\ \quad|\\ \mathrm{O{=}C{-}NHOH}\end{array}$

XII

could not form a chelate.

Nef (200) reported formohydroxamic acid as an unstable compound which decomposed spontaneously at 0°C. Shortly thereafter, Schroeter (266, 268) revealed that he had prepared this acid five years previously and found that it remained unchanged in a vacuum desiccator. Jones (132) reported that the acid was stable if kept in an open container, and underwent decomposition in a sealed tube. From the decomposition of formohydroxamic acid, Schroeter obtained carbon dioxide and ammonia, while Jones obtained carbon monoxide and hydroxylamine. The latter observation was probably the correct one, since the reaction of carbon monoxide with hydroxylamine yielded formohydroxamic acid (141). Since it was well known that formohydroxamyl chloride, HCCl=NOH, when treated with alkali gave fulminic acid (198), it was expected that formohydroxamic acid, if it had the structure HC(OH)=NOH, would lose water to yield the same product. No fulminic acid was obtained, and formohydroxamic acid was assigned the structure (132, 133, 200, 201) shown below:

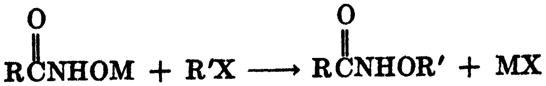


$$\mathrm{H\overset{\displaystyle O}{\overset{\|}{C}}{-}N\begin{matrix}\diagup H\\ \diagdown OH\end{matrix}}$$

It should be noted that benzyl formohydroxamate (XIV), when treated with phosphorus pentachloride, yielded benzyl formohydroxamyl chloride (XV). This reaction can best be shown by attributing to XIV the hydroxyoxime structure.

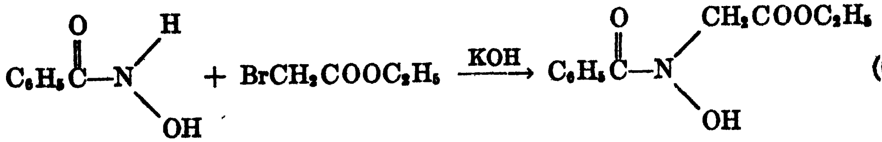
$$\underset{\substack{\text{XIV}\\ \text{Benzyl formohydroxamate}}}{\mathrm{HC(OH){=}NOCH_2C_6H_5}} + \mathrm{PCl_5} \longrightarrow \underset{\substack{\text{XV}\\ \text{Benzyl formohydroxamyl}\\ \text{chloride}}}{\mathrm{HCCl{=}NOCH_2C_6H_5}} + \mathrm{HCl} + \mathrm{POCl_3} \qquad (4)$$

The structure of the alkylated monohydroxamic acids was similarly concerned with the existence of isomeric forms of the same compound. When monohydroxamic acids were alkylated, *O*-alkyl derivatives were formed.



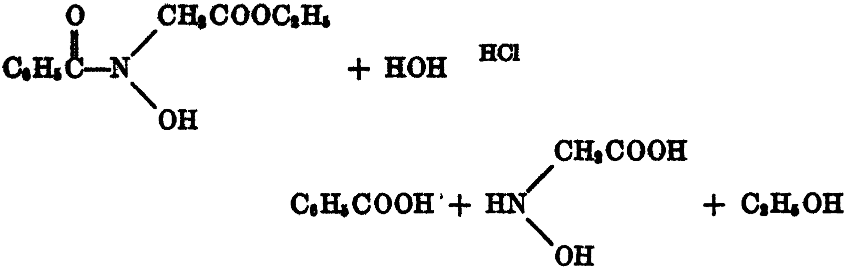
$$\mathrm{R\overset{\displaystyle O}{\overset{\|}{C}}NHOM} + \mathrm{R'X} \longrightarrow \mathrm{R\overset{\displaystyle O}{\overset{\|}{C}}NHOR'} + \mathrm{MX} \qquad (5)$$

N-Alkyl derivatives were probably formed simultaneously (122). Some confirmation for this lies in the single report that benzohydroxamic acid and ethyl



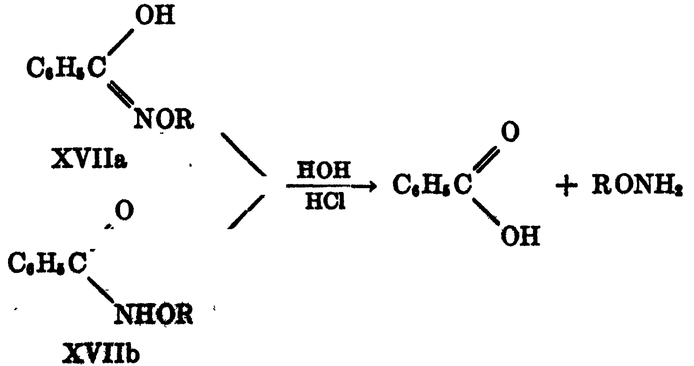
$$\mathrm{C_6H_5\overset{\displaystyle O}{\overset{\|}{C}}{-}N\begin{matrix}\diagup H\\ \diagdown OH\end{matrix}} + \mathrm{BrCH_2COOC_2H_5} \xrightarrow{\mathrm{KOH}} \underset{\text{XVI}}{\mathrm{C_6H_5\overset{\displaystyle O}{\overset{\|}{C}}{-}N\begin{matrix}\diagup CH_2COOC_2H_5\\ \diagdown OH\end{matrix}}} \qquad (6)$$

bromoacetate in the presence of alcoholic potassium hydroxide yielded carboethoxymethyl benzohydroxamic acid (XVI), which upon hydrolysis gave α-hydroxyaminoacetic acid (153).



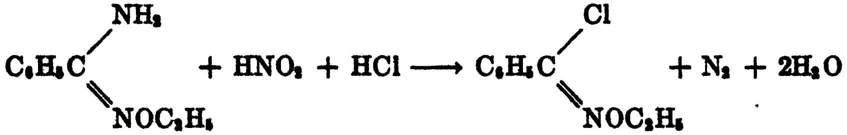
(7)

The hydrolysis of alkyl benzohydroxamates (XVIIa and XVIIb) yielded benzoic acid and *O*-alkylhydroxylamines (55, 175, 299). Lossen (175) maintained that this reaction could be explained only by structure XVIIa. This claim was not valid, since in the hydrolytic cleavage of the carbon–nitrogen bond, the hydrogen of the water was found attached to the nitrogen atom, while the oxygen atom *or* hydroxyl group was attached to the carbon atom (134). Thus, either XVIIa or XVIIb gave the same products.



(8)

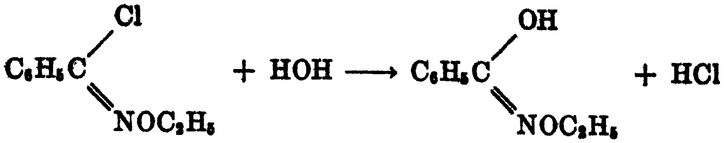
Tiemann (287–289, 291, 292) and Hofmann (112) attempted to prepare compounds of the XVIIa type by the direct substitution of the —NH_2 group in the amino form (XVIII) of *O*-ethylbenzamidoxime. With nitrous acid, in the presence of an excess of hydrochloric acid, the product was ethyl benzohydroxamyl chloride (XIX) which, although unusually stable, could be hydrolyzed to ethyl benzohydroxamate (XX) (231, 311, 313).



(9)

XVIII
O-Ethylbenzamidoxime

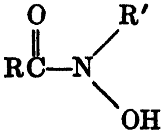
XIX
Ethyl benzohydroxamyl chloride



XX
Ethyl benzohydroxamate

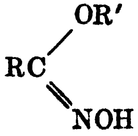
Compound XX was identified as ethyl benzohydroxamate by conversion to a diethyl benzohydroxamate derivative identical with the product obtained by the ethylation of ethyl benzohydroxamic acid or of ethyl benzohydroxamate. When sulfuric acid replaced the hydrochloric acid in equation 9, the products were benzoic acid and *O*-ethylhydroxylamine. Since ethyl benzohydroxamate, when prepared by other methods, was stable under the conditions employed with the sulfuric acid, it was assumed that XVIIb was the stable form, while XVIIa was an intermediate reactive form. This view, expressed by Tiemann, made possible the existence of XVIIa, momentarily, after which it rearranged to the stable form. This was indicated by Krüger (159), who obtained ethyl benzohydroxamate directly from XVIII by utilizing low temperatures and one equivalent of sodium nitrite, in the presence of sulfuric acid.

Compounds of the type



XXI

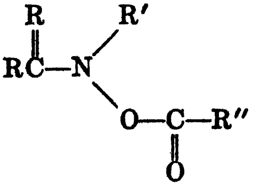
or



XXII

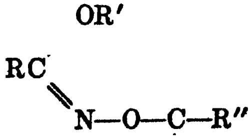
have been prepared by methods which may be described as indirect. The reaction between an *N*-alkyl(or aryl)hydroxylamine, R′NHOH, and an acyl halide yielded a compound capable of existing in one form, R′N(COR)OH. This type of compound, since it was soluble in ammonia, alkali hydroxide, and sodium carbonate, and gave the characteristic color of the monohydroxamic acids with ferric chloride, was indistinguishable from derivatives which were capable of existing as the isomeric forms XXI and XXII (29, 32, 45, 46, 95).

The probable existence of compounds which possessed structures XXI and XXII stemmed directly from their mode of preparation. They were prepared by the alkaline hydrolysis of alkyl aroyl monohydroxamates, which existed as the isomers



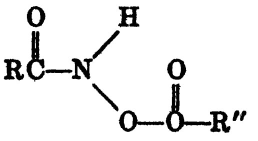
XXIIIa

and

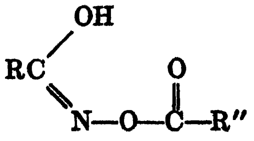


XXIIIb

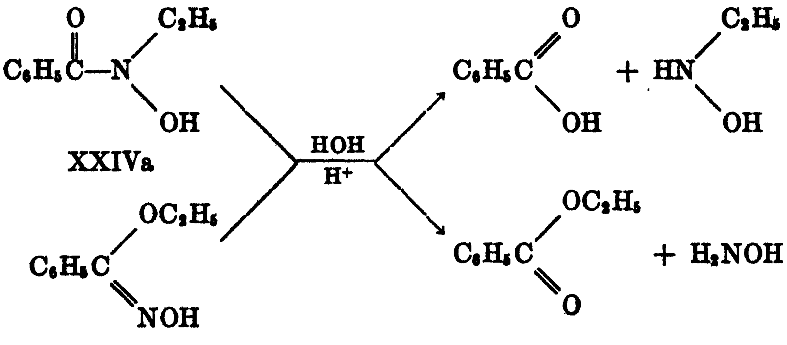
It may be noted that the aroyl group was cleaved first by alkaline hydrolysis. The behavior of XXIIIa and XXIIIb on acid hydrolysis was normal; the products obtained were



or



The hydrolysis of alkyl benzohydroxamic acids in acid solution yielded an alkyl benzoate and hydroxylamine (96, 120, 175, 177). This indicated that the metastable form (XXIVb) was the reactive one.



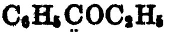
XXIVa

XXIVb

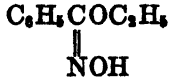
(10)

Such evidence cannot be considered critical; no attempt was made to search for traces of *N*-ethylhydroxylamine.

Ethyl benzohydroxamic acid was found to exist in two forms, an *α*-form (XXVa), melting at 53.5°C., and a *β*-form (XXVb), melting at 67.5–68°C. (96, 186). The former was completely soluble in alkali, while the latter was insoluble. On hydrolysis in acid solution each yielded the same products, ethyl benzoate and hydroxylamine. Lossen (177) and Gürke (96) believed that these were polymorphous manifestations of the same compound. Werner (306) suggested instead that they were *syn*- and *anti*-forms.



$C_6H_5\underset{\cdot\cdot}{C}OC_2H_5$



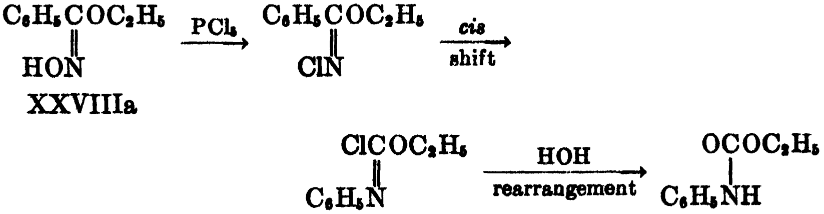
$C_6H_5\underset{\underset{NOH}{\|}}{C}OC_2H_5$

XXVa	XXVb
Ethyl *syn*-benzohydroxamic acid	Ethyl *anti*-benzohydroxamic acid
(*α*)	(*β*)

Each gave a different acetyl and *p*-nitrobenzyl derivative (305).

Lossen (182) prepared methyl benzohydroxamic acid and reported two forms, one melting at 65°C. (XXVIa) and the other at 101°C. (XXVIb). Werner (309) obtained two forms of the same compound, one melting at 44°C. (XXVIIa), the other at 65°C. (XXVIIb). Three forms of methyl benzohydroxamic acid were indicated. In order to show that two of the forms were identical, Werner first obtained a sample of XXVIb from Lossen and then proceeded to check the preparation of XXVIIb. When he recrystallized this latter product and XXVIb from ligroin, both compounds melted at 101°C. Even the residues in the flask melted at 101°C. Werner again prepared XXVIIb, melting at 65°C., in a different room. When XXVIIb was brought into the room in which the recrystallizations had been carried out previously, the product melted at 101°C. It appeared that XXVIIb was a metastable physical form of XXVIb; hence only two stable forms of methyl benzohydroxamic acid were actually present.

Werner (305, 306, 309, 318) further developed the hypothesis that geometric isomerism existed amongst the alkyl benzohydroxamic acids. When the α-form of ethyl benzohydroxamic acid (XXVIIIa) was treated with phosphorus pentachloride and hydrolyzed, there was obtained ethyl phenylcarbamate. The mechanism of this reaction was assumed to be as follows:[1]

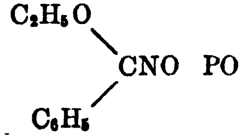


$$\underset{HON}{\overset{C_6H_5COC_2H_5}{\|}} \xrightarrow{PCl_5} \underset{ClN}{\overset{C_6H_5COC_2H_5}{\|}} \xrightarrow[\text{shift}]{cis} \underset{C_6H_5N}{\overset{ClCOC_2H_5}{\|}} \xrightarrow[\text{rearrangement}]{HOH} \underset{C_6H_5NH}{\overset{OCOC_2H_5}{|}} \qquad (11)$$

XXVIIIa

(11)

The β-form (XXVIIIb) after identical treatment gave the phosphate:



XXIX

Werner and Subak (318) obtained related products with the α- and β-forms of methyl benzohydroxamic acid. Houben and Pfankuch (118) reported that ethyl *anti*-formohydroxamic acid yielded a product similar to XXIX when treated with phosphorus pentachloride. Douglas (69) prepared ethyl *anti*-thenohydroxamic acid. Werner (305) pointed out that, in contrast to other stereoisomeric oximes, these compounds were not converted into one another by chemical reactions. Ethyl acetyl benzohydroxamate, melting point 38–39°C. (from ethyl *syn*-benzohydroxamic acid), was stable up to 140°C.; when it was treated with alcoholic sodium hydroxide, ethyl *syn*-benzohydroxamic acid was again obtained. The acetylated ethyl *anti*-benzohydroxamic acid demonstrated a similar stability. Benzohydroxamyl chloride was expected to exist in *syn*- and *anti*-forms, but Werner (307) was unable to separate the two. Werner and Buss (313) found that the two isomeric benzaldoximes did not yield two isomeric benzohydroxamyl chlorides.

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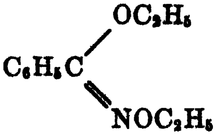
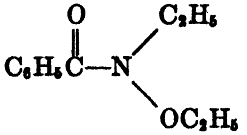
[1] Recent work shows that the Beckmann rearrangement does not involve a *cis* shift of groups (Gilman: *Organic Chemistry*, Vol. I, p. 471, John Wiley and Sons, Inc., New York (1943)); hence the above configuration of XXVIIIa should probably be reversed.

The problem of structure was also present amongst the dialkylated monohydroxamic acids. Lossen (178) showed that the product (XXX) obtained by the interaction of *N*-ethyl-*O*-ethylhydroxylamine and benzoyl chloride was different from the product obtained by the alkylation of benzohydroxamic acid. The latter could exist as either



XXXIa

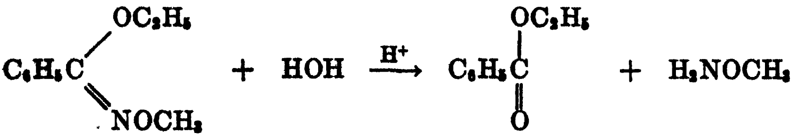
or



XXXIb

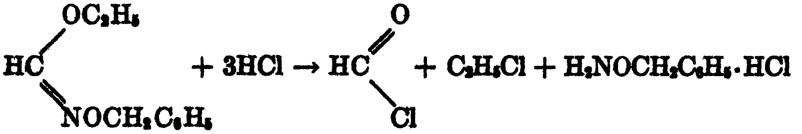
Since XXX would have the structure XXXIb, this was an argument in favor of structure XXXIa for the hydroxamic acid derivatives obtained by the direct alkylation of the monohydroxamic acids (287).

Additional evidence was presented by Arndt and Scholz (21), who found that benzohydroxamic acid and diazomethane gave a product which contained two methoxyl groups. There was no indication of the presence of an $=NCH_3$ linkage. The hydrolysis of ethyl methyl benzohydroxamate (XXXII) (prepared by the alkylation of benzohydroxamic acid) yielded *O*-methylhydroxylamine and ethyl benzoate, indicating a structure related to XXXIa. Similarly, methyl ethyl benzohydroxamate gave *O*-ethylhydroxylamine and methyl benzoate (186). The two forms of ethyl benzyl formohydroxamate (XXXIII), when subjected to the action of hydrogen chloride, yielded *O*-benzylhydroxylamine and ethyl chloride (50).



(12)

XXXII
Ethyl methyl
benzohydroxamate



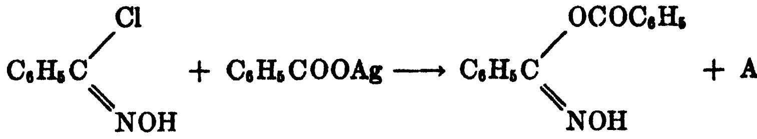
(13)

XXXIII
Ethyl benzyl
formohydroxamate

It was interesting to note that ethyl benzohydroxamic acid and ethyl benzohydroxamate on alkylation yielded the same diethyl benzohydroxamate, and with dilute acid each yielded *O*-ethylhydroxylamine and ethyl benzoate (178).

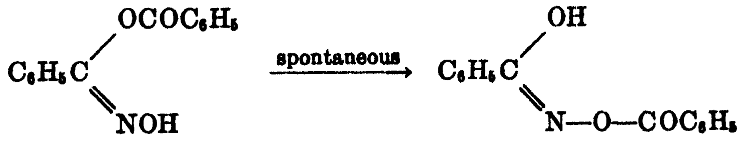
It was mentioned previously (page 213) that Jones (132) had isolated benzoyl acetohydroxamate in two forms, a metastable form melting at 69–70°C. (XIa) and a stable form melting at 98–99°C. (XIb). Cameron (60) studied these crystalline modifications and observed that while the latter form was the more stable, it was converted into the former with the absorption of heat. Since XIa was the possessor of the greater energy, it was the more reactive form. This observation was in agreement with other observations concerning the structure of the reactive form of the hydroxamic acids.

The structure RC(=NOH)OCOR′ was found to be unstable. When silver benzoate and benzohydroxamyl chloride were allowed to react, the product first isolated melted at 95°C. (XXXIV) (313, 317). On repeated crystallization, the melting point was raised to 161°C., similar to that of benzoyl benzohydroxamate. This same phenomenon was observed when XXXIV was allowed to remain without further treatment. After 2 hr. the melting point was 103°C., and after two days, 158–161°C. The reactions occurring in this transformation appeared to involve a rearrangement.



(14)

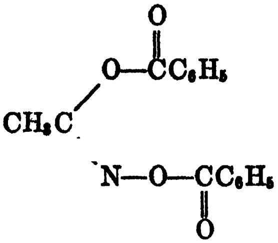
XXXIV

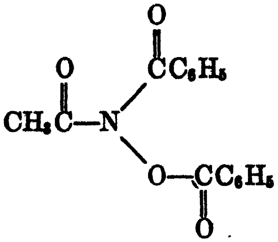


(15)

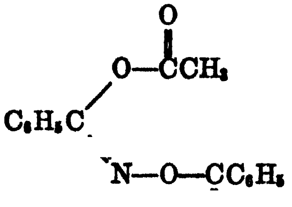
The triacylated hydroxylamines were found to be polymorphous. Dibenzoyl benzohydroxamate, for example, existed in three forms: the α-form, melting at 100°C.; the β-form, melting at 141°C.; and the γ-form, melting at 112°C. (171, 182). In their chemical behavior the three forms were identical, differing only in the relative ease with which the reactions proceeded (171, 182). Lehmann (161) studied the three crystalline modifications and observed that when a melt of the β-form was cooled, the α-form crystallized first and was then transformed into the β-form. The melt of the γ-form, on slow cooling, yielded the α-form. Only by the intense heating of the γ-modification was the β-form obtained. When a mixture of the α- and β-forms was warmed carefully, the latter crystals grew at the expense of the former, until the α-modification had entirely disappeared. Lossen (181) obtained the β-form by heating the γ-form with dilute hydrochloric acid. This evidence indicated that the β-, or highest melting, form was the most stable, an observation in keeping with the general rule with polymorphous compounds.

Jones (132, 135) presented favorable evidence for the existence of the isomeric triacylated hydroxylamine derivatives. The reaction between sodium *aci*-nitroethane and benzoyl chloride yielded a neutral product which with alcoholic potassium hydroxide gave a mixture of benzoyl benzohydroxamate (XXXV), benzoyl acetohydroxamate (XXXVI), benzoic acid, and ethyl benzoate. These products indicated a mixture of the two isomeric compounds XXXVIIa and XXXVIIb.

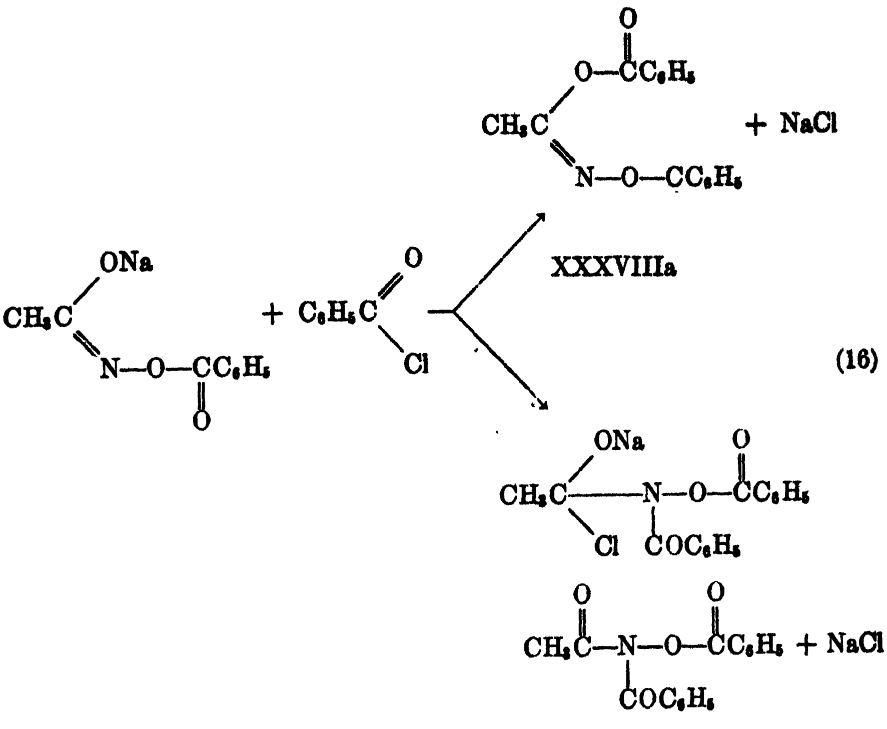

XXXVIIa


XXXVIIb

XXXV could be derived from XXXVIIb by cleavage of the acetyl group; XXXVI was obtained from XXXVIIa, where the acetyl group, *per se*, did not exist, so that a benzoyl group was cleaved instead. The assumption in the formation of XXXV was that the acetyl group was cleaved before the benzoyl group. In addition, when sodium benzoyl acetohydroxamate and benzoyl chloride were allowed to react, two products were obtained, an oil (XXXVIIIa) and a crystalline material (XXXVIIIb) melting at 69–70°C. With alcoholic potassium hydroxide, XXXVIIIb gave benzoyl benzohydroxamate, acetic acid, and ethyl acetate, while XXXVIIIa gave benzoyl acetohydroxamate, benzoic acid, and ethyl benzoate. Two products were obtained also when potassium benzoyl benzohydroxamate and acetyl chloride were allowed to react. One, melting at 69–70°C., was shown to be identical with XXXVIIIb; with alcoholic potassium hydroxide it yielded benzoyl benzohydroxamate. The other, higher melting product was assumed to be



Jones believed that the reaction between sodium benzoyl acetohydroxamate and benzoyl chloride proceeded either by direct replacement to yield XXXVIIIa or indirectly to yield XXXVIIIb.

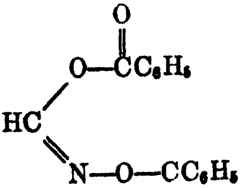


XXXVIIIa

(16)

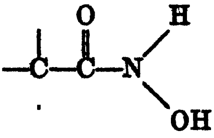
XXXVIIIb

It should be noted with regard to such a mechanism that sodium *aci*-nitromethane and benzoyl chloride yielded a neutral product which on treatment with alcoholic potassium hydroxide gave only benzoyl formohydroxamate, $HC(OH)=NOCOC_6H_5$, and benzoic acid. Apparently no addition occurred here. In a similar fashion, sodium benzoyl formohydroxamate and benzoyl chloride gave only



since on hydrolysis with alcoholic potassium hydroxide, no benzoyl benzohydroxamate was found.

The discussion which has been presented up to this point on the structure of the hydroxamic acids has been concerned with the derivatives which contain the system



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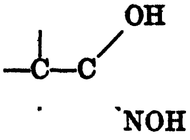
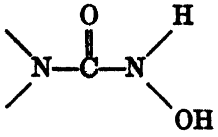


An interesting group of compounds, the hydroxyureas or carbamylhydroxamic acids, contain the



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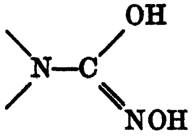
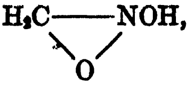


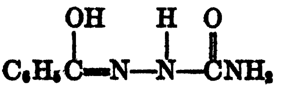
structure. Hurd (121) first pointed out that such compounds bear a striking similarity to the hydroxamic acids.

As an alternative to the tautomeric concept of the structure of the monohydroxamic acids, Oddo (204, 205) proposed the "mesohydric" structure. Palazzo and Oliveri-Mandala (208–214) suggested the cyclic structure,  for formohydroxamic acid. Such proposals offer no fundamental clarification of the many questions which remain unanswered relative to the structure of the hydroxamic acids.

D. MONOHYDROXAMIC ACIDS

In aqueous solution the monohydroxamic acids behave as weak acids: acetohydroxamic acid, for example, has an ionization constant of 0.28×10^{-7} (94, 208). The monohydroxamic acids can be titrated with alkali, using phenolphthalein as the indicator (219). They reduce Fehling's solution. Their most characteristic reaction is the intense dark violet color produced with ferric chloride. With cupric acetate, characteristic green-blue insoluble copper salts are formed. This reaction is frequently utilized in the isolation and purification of the monohydroxamic acids.

Many of the reactions of the monohydroxamic acids will be discussed in other sections of this review. A few reactions may be mentioned here. With aniline (193) or with benzenediazonium chloride (236), benzohydroxamic acid gave benzanilide. Semicarbazide and benzohydroxamic acid yielded



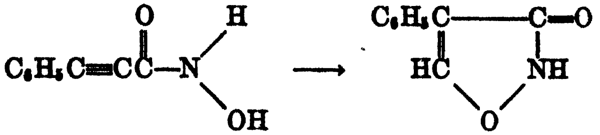
$$C_6H_5\overset{\overset{OH}{|}}{C}{=}N{-}\overset{\overset{H}{|}}{N}{-}\overset{\overset{O}{\|}}{C}NH_2$$

a tautomer of benzoylsemicarbazide (256). This exchange was not a general reaction, since salicylohydroxamic and cinnamohydroxamic acids did not react.

Hypobromous acid and the monohydroxamic acids reacted as shown in equation 17 (216, 217).

$$2RCONHOH + 2HOBr \rightarrow 2RCOOH + 2HBr + N_2O + H_2O \quad (17)$$

Acetohydroxamic acid with nitrous acid yielded acetic acid and nitrous oxide (101). The reduction of monohydroxamic acids with sodium-mercury amalgam led to the formation of amides (86). This reaction was the reverse of the oxidation of amides to hydroxamic acids, either with Caro's reagent or with hydrogen peroxide (210). Ruhemann and Stapelton (255) found that phenylpropiolohydroxamic acid (XXXIX) could not be isolated, since it underwent cyclization to 5-phenyl-3-isoxazolone (XL).

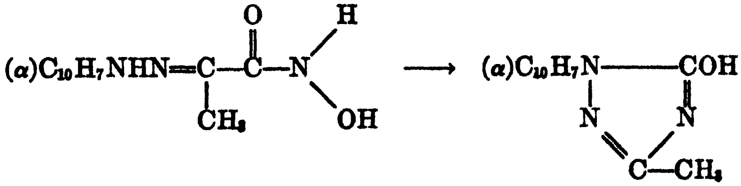


XXXIX XL

5-Phenyl-3-isoxazolone

(18)

Pickard and Neville (221) showed that the product was the hydroxamic acid, by comparing the properties of its benzoyl derivative with those of 5-phenyl-3-benzoylisoxazolone. In the presence of dilute mineral acids pyruvylohydroxamic acid was converted into the oxime of pyruvic acid (94). The arylhydrazones of pyruvylohydroxamic acid were readily converted into triazole derivatives (93).



(19)

Monohydroxamic acids have been proposed recently as flotation agents for certain copper ores (104).

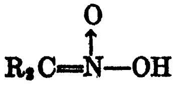
Preparation

The monohydroxamic acids have been prepared by many methods. The most general is the reaction between an ester and hydroxylamine. Other methods, although satisfactory in certain instances, have limited application.

The methods which have been utilized for the preparation of monohydroxamic acids are:

(*1*) *The reaction between an ester and hydroxylamine:* The reaction between an ester and hydroxylamine in absolute alcohol proceeds rapidly at room temperature, particularly in the presence of an equimolecular quantity of sodium alkoxide (16, 56, 57, 99, 127–131, 147, 197, 221, 239, 247). In the absence of the alkaline reagent longer periods of time are required (131, 140). The reaction may be carried out in water, sodium carbonate replacing the sodium alkoxide (195).

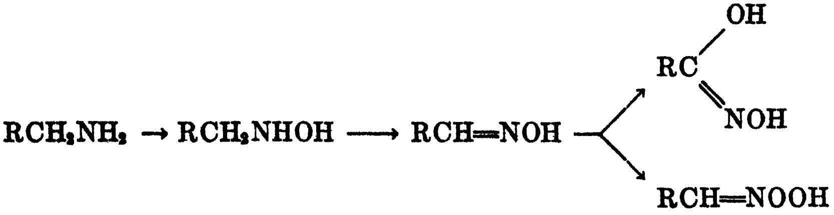
(2) *The oxidation of aldoximes, amines, aldehyde-ammonias, amides, and nitriles:* The reaction between Caro's reagent (persulfuric acid, $H_2S_2O_8$) and benzaldoxime gave, amongst other products, benzohydroxamic acid (26). The reaction appeared to be of general application with oximes (36). Ketoximes and Caro's reagent yielded nitronic acids (38):



$$R_2C{=}\overset{\overset{\displaystyle O}{\uparrow}}{N}{-}OH$$

Hydrogen peroxide can replace persulfuric acid in these oxidations (210).

The oxidation of primary amines by persulfuric acid yielded hydroxamic acids (27, 28, 37). Amines of the general formulas RCH_2NH_2 and R_2CHNH_2 and certain amino acids were successfully oxidized. The presence of hydroxamic acids was determined by the color test with ferric chloride. The reaction probably proceeded through several intermediates (26). No reaction occurred with aminosulfonals, aminovaleric acid, glutamine, and cystine.



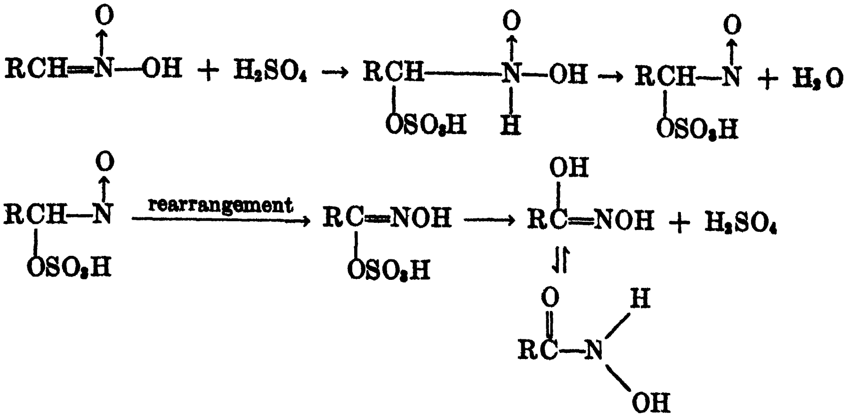
$$RCH_2NH_2 \rightarrow RCH_2NHOH \longrightarrow RCH{=}NOH \begin{cases} \nearrow RC{\overset{\diagup OH}{\underset{\diagdown\!\diagdown NOH}{}}} \\ \searrow RCH{=}NOOH \end{cases} \qquad (20)$$

Tests with tyrosine and glutamic acid were doubtful. In some instances it was necessary to heat the reactants in order to have oxidation proceed at a fairly rapid rate. Secondary amines were also oxidized to products which gave a positive color test for monohydroxamic acids; as a result, the reaction could not be utilized to distinguish primary from secondary amines (28, 37).

Acetaldehyde-ammonia was oxidized by persulfuric acid to acetohydroxamic acid (39). The oxidation of amides by means of hydrogen peroxide was successful in a few cases (210). Benzamide and toluamide were oxidized to the corresponding monohydroxamic acids; the reaction failed with acetamide, propionamide, and oxamide. Nitriles, when oxidized with hydrogen peroxide, yielded hydroxamic acids.

(3) *The rearrangement of nitroparaffins by mineral acids:* Victor Meyer (192) found that heating nitroparaffins with hydrochloric acid in sealed tubes gave hydroxylamine as one of the products. He correctly surmised that the intermediate product was a hydroxamic acid. This was confirmed by later workers (30, 35, 61, 83, 240, 241). 1-Nitropropane and anhydrous sulfuric acid gave propionohydroxamic acid in 50 per cent yield; this process has recently been patented (164, 165).

The mechanism of the rearrangement of *aci*-nitroparaffins into the tautomeric forms of the monohydroxamic acids is not well understood. One mechanism assumes the addition of hydrochloric acid or sulfuric acid to the *aci*-nitroalkane, followed by loss of water and rearrangement (104, 202).

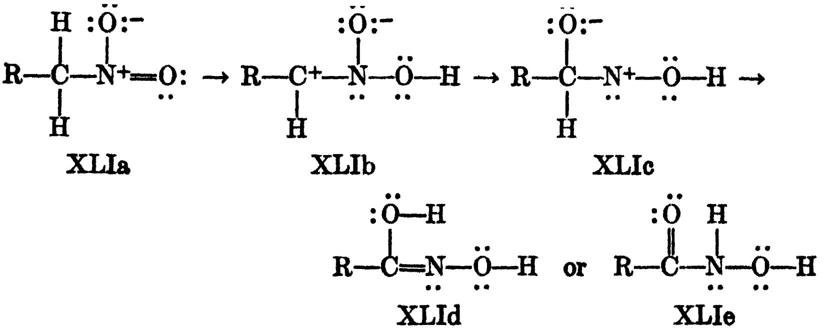


$$\mathrm{RCH{=}\overset{\overset{O}{\uparrow}}{N}{-}OH + H_2SO_4 \rightarrow \underset{OSO_3H}{RCH}{-}\underset{H}{\overset{\overset{O}{\uparrow}}{N}}{-}OH \rightarrow \underset{OSO_3H}{RCH}{-}\overset{\overset{O}{\uparrow}}{N} + H_2O}$$

$$\mathrm{\underset{OSO_3H}{RCH}{-}\overset{\overset{O}{\uparrow}}{N} \xrightarrow{rearrangement} \underset{OSO_3H}{RC}{=}NOH \longrightarrow \overset{OH}{RC}{=}NOH + H_2SO_4 \rightleftharpoons R\overset{O}{\overset{\|}{C}}{-}N\begin{smallmatrix}H\\ OH\end{smallmatrix}} \qquad (21)$$

Junell (149) studied the kinetics of the reaction and found it to be monomolecular. The rate-determining step was the rearrangement of the *aci*-form to the hydroxamic acid and was very rapid when compared with the relative slowness with which the nitroparaffin was converted into the *aci*-form. In the presence of bromine, the product obtained was the bromonitroparaffin, $RCHBrNO_2$, since the addition of bromine to the *aci*-form was faster than the rearrangement to the hydroxamic acid.

The rearrangement was indicated by Hurd (122) to proceed as follows:



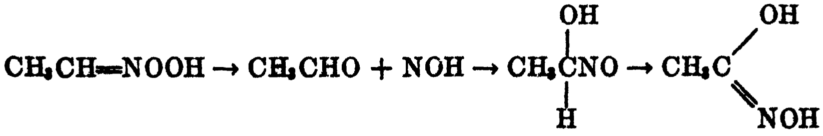
$$\mathrm{R{-}\underset{H}{\overset{H}{C}}{-}\overset{:\ddot{O}:^-}{N^+}{=}\ddot{O}: \rightarrow R{-}\underset{H}{C^+}{-}\overset{:\ddot{O}:^-}{\ddot{N}}{-}\ddot{O}{-}H \rightarrow R{-}\underset{H}{\overset{:\ddot{O}:^-}{C}}{-}\ddot{N}^+{-}\ddot{O}{-}H \rightarrow}$$

XLIa XLIb XLIc

$$\mathrm{R{-}\overset{:\ddot{O}{-}H}{C}{=}\ddot{N}{-}\ddot{O}{-}H \;\; or \;\; R{-}\overset{:\ddot{O}}{\overset{\|}{C}}{-}\overset{H}{\ddot{N}}{-}\ddot{O}{-}H} \qquad (22)$$

XLId XLIe

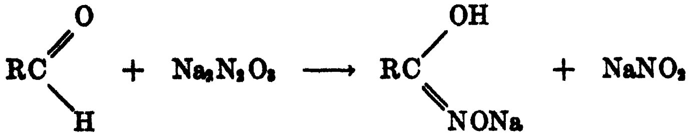
According to this view, XLIb represented an unstable condition, a carbon sextet. The carbon atom appropriated electrons from the neighboring oxygen, which had a surplus, and this initiated the molecular rearrangement to XLIc and led eventually to LXId or XLIe. Steinkopf and Jürgens (278) considered the rearrangement as one involving the formation of free nitrosyl.



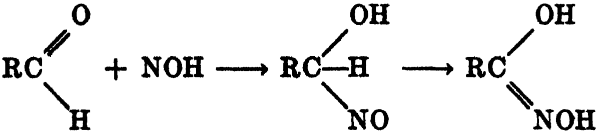
$$\mathrm{CH_3CH{=}NOOH \rightarrow CH_3CHO + NOH \rightarrow CH_3\underset{H}{\overset{OH}{C}}NO \rightarrow CH_3C\begin{smallmatrix}OH\\ NOH\end{smallmatrix}} \qquad (23)$$

In this connection, it should be noted that neutral nitromethane, when subjected to ultraviolet radiation, rearranged to formohydroxamic acid, while formohydroxamic acid, under similar irradiation, partially rearranged to *aci*-nitromethane (40, 41). The distillation of phenylnitromethane at atmospheric pressure yielded benzoyl benzohydroxamate (107). In all probability the rearrangement possesses a mechanism more complex than any of those proposed.

(*4*) *The reaction between an aldehyde and compounds capable of yielding free "nitrosyl":* In the course of an investigation into new methods for the preparation of monohydroxamic acids, Angeli (1, 2, 4) prepared sodium nitrohydroxamate, $Na_2N_2O_3$. With certain aldehydes, this salt yielded the sodium salt of monohydroxamic acids. In practice, the sodium nitrohydroxamate, in aqueous solution, was added to the aqueous or alcoholic solution of the aldehyde. An exothermic reaction ensued, and following this, acidification yielded the monohydroxamic acid (4–13, 59, 90). No reaction occurred in anhydrous ether (59). Many aldehydes did not react, e.g., salicylaldehyde, *o*-nitrobenzaldehyde, and pyrrolaldehyde. Glucose and lactose were also unreactive (11, 18, 19).


(24)

The reaction was shown to proceed *via* the formation of a nitroso alcohol by a 1,2-addition of free nitrosyl to the carbonyl group of the aldehyde. Although Angeli did not report the formation of a transitory blue-green color in the course of this reaction, the color, indicative of the presence of nitroso alcohols, was observed by others (34, 35, 41, 42, 278, 279), particularly when methyl acetate or acetone was added to the aqueous reaction mixture. Potassium nitrosyl, NOK, a product of the photoreduction of nitrates, was proposed as the intermediate which reacted with photosynthesized formaldehyde to yield formohydroxamic acid, the first step in the phytosynthesis of the nitrogen compounds found in plants (25, 40–43).


(25)

Benzenesulfonhydroxamic acid, Piloty's Acid, $C_6H_5SO_2NHOH$, and certain aldehydes reacted to form monohydroxamic acids (3, 4, 14–16, 62, 63, 251, 252, 296). The procedure employed was to mix equimolecular quantities of benzenesulfonhydroxamic acid with an aldehyde in water or alcohol, and to add alkali until the mixture was alkaline. Upon acidification, the monohydroxamic acid was obtained. Many aldehydes did not react (4, 16, 18, 228).

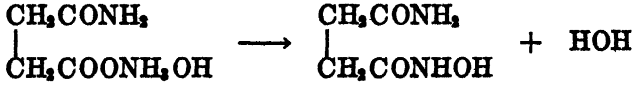
(*5*) *The reaction between an amide and hydroxylamine:* Aliphatic and aromatic amides reacted with hydroxylammonium chloride at moderate temperatures

(20–100°C.) to yield monohydroxamic acids (79, 110, 111). The yield with acetamide was reported as quantitative. Benzamide did not react.

(*6*) *The reaction between an acid anhydride or acid halide and hydroxylamine:* Acetic anhydride and hydroxylamine, or its salts, yielded acetohydroxamic acid (64, 65, 73, 97, 194). Acid halides and hydroxylamine, in the presence of alkali, gave, in addition to the monohydroxamic acid, further acylated products (108, 169). In some instances, this method was to be preferred over Method 1, e.g., in the preparation of 2,4-dihydroxybenzohydroxamic acid (270).

An improved procedure employed two equivalents of free hydroxylamine and one of the acid halide in benzene or ether (136, 137, 143).

(*7*) *The pyrolysis of hydroxylammonium salts of organic acids:* W. Lossen (168), in 1868, prepared several hydroxylammonium salts of organic acids but neglected to study their pyrolysis. Ssabonev (275) found that hydroxylammonium succinamate (XLII), when heated to its melting point, or when allowed to stand,

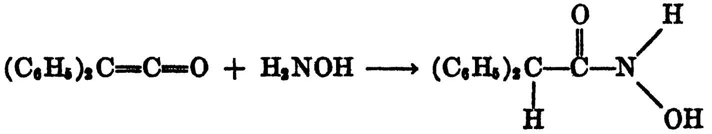


$$\begin{array}{l}CH_2CONH_2\\ |\\ CH_2COONH_3OH\end{array} \longrightarrow \begin{array}{l}CH_2CONH_2\\ |\\ CH_2CONHOH\end{array} + HOH \tag{26}$$

XLII

gave a hydroxamic acid. Jones and Oesper (141) found that hydroxylammonium formate decomposed slowly during a period of several weeks, or more rapidly when heated, to formohydroxamic acid. The method was not of general application (121a, 148).

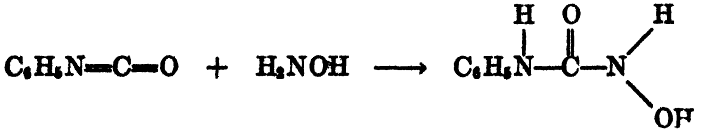
(*8*) *The reaction between ketenes and hydroxylamine:* The preparation of monohydroxamic acids by the reaction between ketenes and hydroxylamine was first proposed by Staudinger (276). Jones and Hurd (136) found that diphenylketene and hydroxylamine gave diphenylacetohydroxamic acid. With an excess of the ketene, the acylation continued until the triacylated hydroxylamine was



$$(C_6H_5)_2C{=}C{=}O + H_2NOH \longrightarrow (C_6H_5)_2\underset{\displaystyle H}{\underset{|}{C}}-\overset{\displaystyle O}{\overset{\|}{C}}-N\begin{array}{l}\diagup H\\ \diagdown OH\end{array} \tag{27}$$

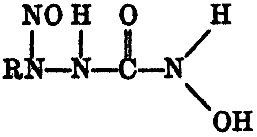
formed. The yields of mono-, di-, and tri-acylated hydroxylamines were excellent. It was interesting to observe that two acyl groups were readily introduced into the monohydroxamic acid with a ketene, while with acid anhydrides the last acyl group was introduced with some difficulty (29, 124, 125).

A related reaction was that between an isocyanate and hydroxylamine which led to the formation of carbamylhydroxamic acids possessing the structure, RNHCONHOH or RNHC(OH)=NOH (44, 77, 121, 124, 150, 154).



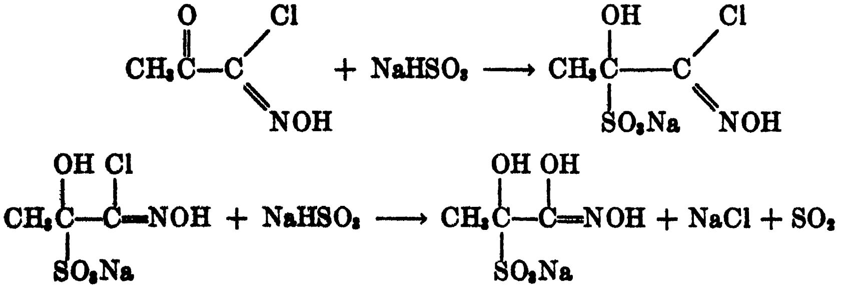
$$C_6H_5N{=}C{=}O + H_2NOH \longrightarrow C_6H_5\overset{\displaystyle H}{\overset{|}{N}}-\overset{\displaystyle O}{\overset{\|}{C}}-N\begin{array}{l}\diagup H\\ \diagdown OH\end{array} \tag{28}$$

Quilico and Justoni (243, 244) extended this reaction to prepare compounds of the type,



by the interaction of nitrosocarbohydrazines, RN(NO)N=C=O, and hydroxylamine.

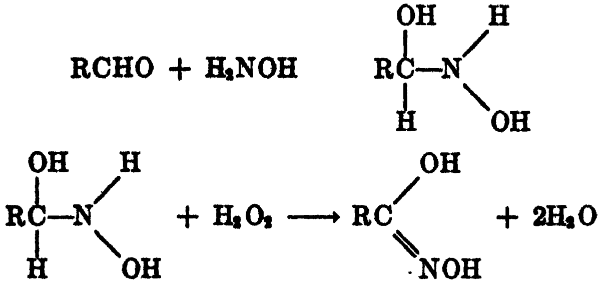
(*9*) *The hydrolysis of monohydroxamyl chlorides:* Ponzio (231) prepared the oxime of *p*-toluoylformohydroxamic acid, *p*-$CH_3C_6H_4C(=NOH)C(=NOH)OH$, by the reaction between the oxime of *p*-toluoylformohydroxamyl chloride and sodium acetate in 50 per cent acetic acid. Pyruvylohydroxamyl chloride first added sodium bisulfite and was then hydrolyzed to the corresponding hydroxamic acid (XLIII) (85, 88).



XLIII

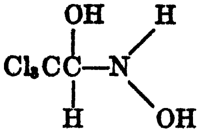
(29)

(*10*) *The reaction between water-soluble aldehydes, hydroxylamine, and hydrogen peroxide:* Water-soluble aldehydes, e.g., formaldehyde, acetaldehyde, and propionaldehyde, when treated with one molecular equivalent of hydroxylamine and two molecular equivalents of hydrogen peroxide, yielded the corresponding hydroxamic acids. The reaction proceeded according to the following equations:



(30)

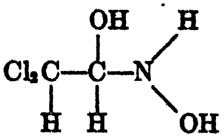
The addition products of chloral and dichloroacetaldehyde with hydroxylamine,



$\mathrm{Cl_3CC(OH)(H)\text{—}N(H)(OH)}$

XLIV

and



$\mathrm{Cl_2C(H)\text{—}C(OH)(H)\text{—}N(H)(OH)}$

XLV

respectively, were isolated (97, 206). From XLIV the principal products were chloroform and formohydroxamic acid and from XLV, dichloromethane and formohydroxamic acid.

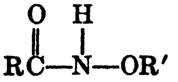
(*11*) *Miscellaneous preparations of monohydroxamic acids:* Ponzio (229, 230) found that $(O_2N)_3CNC_6H_5$ reacted in moist ether to yield phenylazoformohydroxamic acid, $C_6H_5N{=}NCONHOH$. A mixture of methyl alcohol and potassium nitrite when irradiated with ultraviolet light gave formohydroxamic acid (40). Acetohydroxamic acid was obtained by the reaction between acetyl chloride and aromatic isonitroso ketones (274), and by the hydrolysis of acetonitrolic acid, $CH_3C(NO_2){=}NOH$ (322). The reactions between dibenzoyl dichloro-α,α'-furazan and alkali (54), the intermediate nitration product of ethyl furoate and hydroxylamine (187), and α-diketocholanic acid dioxime and nitric acid, yielded products identified as monohydroxamic acids.

Hydroxamic acids have been proposed as intermediates in certain reactions (157, 285).

E. DERIVATIVES OF MONOHYDROXAMIC ACIDS

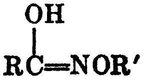
1. *Alkyl- and aryl-substituted monohydroxamic acids*

(a) Compounds of the general formulas



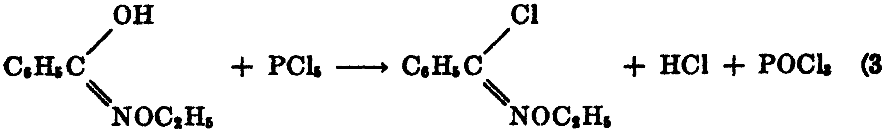
$\mathrm{RC(=O)\text{—}N(H)\text{—}OR'}$

or



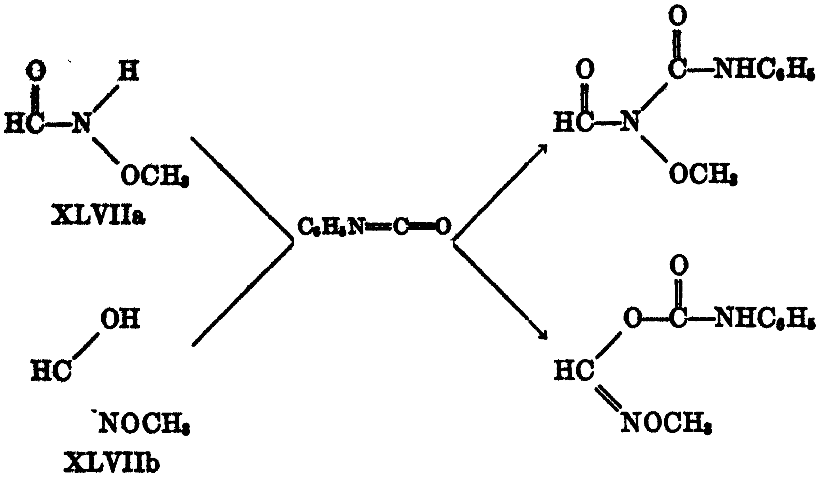
$\mathrm{RC(OH){=}NOR'}$

Compounds of this type are very weak acids; they are liberated from their alkali salts by carbon dioxide. They give no color test with ferric chloride. It was indicated (p. 216) that tautomeric forms were possible with this group of compounds. Thus, ethyl benzohydroxamate and phosphorus pentachloride yielded ethyl benzohydroxamyl chloride, indicating that the reactive form was XLVI (177); on the other hand, methyl formohydroxamate and phenyl isocyanate yielded phenylcarbamoyl methyl formohydroxamate, in the formation of which either XLVIIa or XLVIIb could have reacted (51).



$$\mathrm{C_6H_5C(OH){=}NOC_2H_5 + PCl_5 \longrightarrow C_6H_5C(Cl){=}NOC_2H_5 + HCl + POCl_3} \quad (31)$$

XLVI

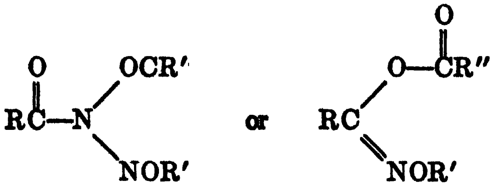


XLVIIa

XLVIIb

(32)

With acyl halides, RCONHOR′ or RC(OH)=NOR′ compounds yielded the isomeric derivatives (222):

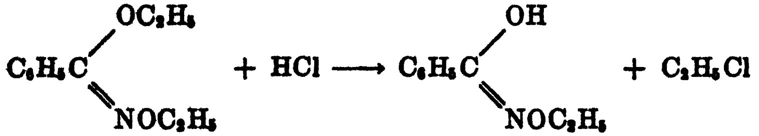


Benzyl formohydroxamate underwent an unusual cleavage with hydrochloric acid to formaldehyde and *O*-benzylhydroxylamine (51).

The monoalkyl- or aryl-substituted monohydroxamic acids have been prepared by the following methods:

(*1*) *The reaction between an alkyl iodide and the alkali metal salt of a monohydroxamic acid:* This reaction was generally carried out in the presence of excess alkali so that the alkali salt was obtained; on treatment with carbon dioxide, the substituted monohydroxamate was liberated (55, 299).

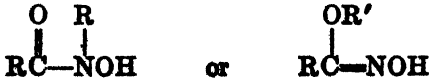
(*2*) *The acid cleavage of a dialkylated monohydroxamic acid:* According to Lossen (182) this method of preparation gave the best yields of alkyl monohydroxamates.



(33)

(*3*) *The alkaline hydrolysis of a compound of the type* RCON(COR″)OR′: Benzoyl ethyl benzohydroxamate on alkaline hydrolysis yielded potassium ethyl benzohydroxamate and potassium benzoate (180).

(b) Compounds of the general formulas

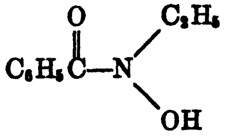


$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\!-\!\overset{\mathrm{R}}{\overset{|}{\mathrm{N}}}\mathrm{OH}$ or $\mathrm{R}\overset{\mathrm{OR'}}{\overset{|}{\mathrm{C}}}\!=\!\mathrm{NOH}$

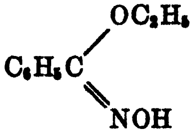
Compounds of this type are stronger acids than the type discussed previously (page 231), since they are soluble in ammonia, alkali hydroxide, and sodium carbonate. They give the characteristic color test of hydroxamic acids with ferric chloride and form copper salts.

Ethyl benzohydroxamic acid was isolated in two forms. The α-modification was acidic, the β-modification neutral toward alkali hydroxides. The two forms have been designated as *cis*- and *trans*-isomers.

Compounds in this group which can exist in either of two isomeric structures are generally prepared by the hydrolysis of a completely substituted hydroxylamine derivative. Thus, ethyl benzohydroxamic acid was prepared by the alkaline or ammoniacal hydrolysis of ethyl benzoyl benzohydroxamate (72, 96, 178) and as a result possessed either structure XLVIIIa or structure XLVIIIb.

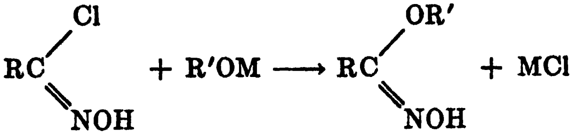


XLVIIIa



XLVIIIb

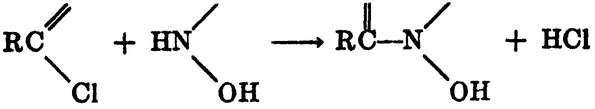
This group of compounds included a small number which, in view of the methods utilized in their preparation, existed in only one structural form. One type was prepared by the interaction of a monohydroxamyl chloride and a metal alkoxide (313, 315), and represented one isomeric form (XLIXa).



XLIXa

(34)

The other type was prepared by the reaction between an *N*-alkyl(or aryl)hydroxylamine with an acid halide, acid anhydride, or ester (29, 31, 32, 45, 46, 146). The product was the other isomeric form (XLIXb).

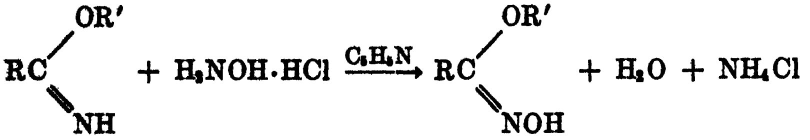


XLIXb

(35)

Other methods employed in the preparation of compounds in this group are as follows:

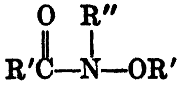
(*1*) *The reaction between an imido ester and hydroxylamine:* The reaction between hydroxylammonium chloride and an imido ester appeared to be of general application for the preparation of compounds of the type RC(OR′)═NOH (118–120, 176, 178, 226, 227).



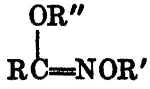
$$RC(OR')\!=\!NH + H_2NOH{\cdot}HCl \xrightarrow{C_5H_5N} RC(OR')\!=\!NOH + H_2O + NH_4Cl \qquad (36)$$

(*2*) *The reaction between an N-alkyl(or aryl)hydroxylamine, potassium alkoxide, and amyl nitrite:* Bamberger and Baudisch (31) obtained phenyl benzohydroxamic acid by the reaction between *N*-phenylhydroxylamine, potassium ethoxide, and amyl nitrite.

(c) Compounds of the general formulas



$R'C(\!=\!O)\!-\!N(R'')\!-\!OR'$ or

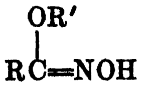


$RC(OR'')\!=\!NOR'$

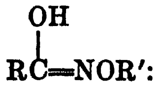
Compounds of this group can exist in a single structural form or as either of two isomeric forms. They possess no acidic properties, do not reduce ammoniacal silver nitrate or Fehling's solution, and give no color test with ferric chloride.

These compounds have been prepared by the following methods:

(*1*) *The alkylation of compounds of the types*

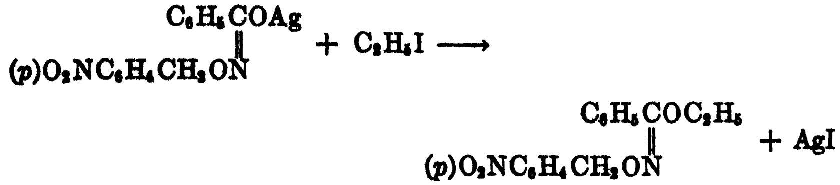


$RC(OR')\!=\!NOH$ *or*

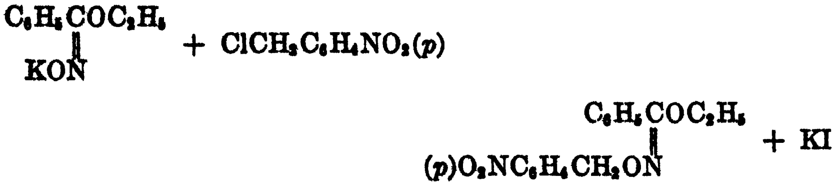


$RC(OH)\!=\!NOR'$:

Werner (305) found that identical ethyl *p*-nitrobenzyl benzohydroxamates were obtained by either of the two methods illustrated in equation 37 or 38.



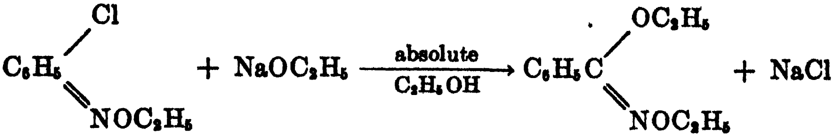
$$(p)O_2NC_6H_4CH_2ON\!=\!C(OAg)C_6H_5 + C_2H_5I \longrightarrow (p)O_2NC_6H_4CH_2ON\!=\!C(OC_2H_5)C_6H_5 + AgI \qquad (37)$$



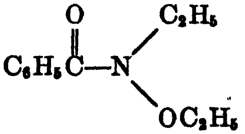
$$KON\!=\!C(OC_2H_5)C_6H_5 + ClCH_2C_6H_4NO_2(p) \longrightarrow (p)O_2NC_6H_4CH_2ON\!=\!C(OC_2H_5)C_6H_5 + KI \qquad (38)$$

Alkyl iodides and alkali hydroxides or alkoxides were used to prepare dialkyl benzohydroxamates from alkyl benzohydroxamic acids (32, 180).

(*2*) *The reaction between an alkyl benzohydroxamyl chloride and sodium alkoxide:* The reaction was used by Tiemann and Krüger (292).


(39)

(*3*) *The reaction between an acid halide and an N-alkyl-O-alkylhydroxylamine:* The reaction between *N*-ethyl-*O*-ethylhydroxylamine and benzoyl chloride yielded diethyl benzohydroxamate:

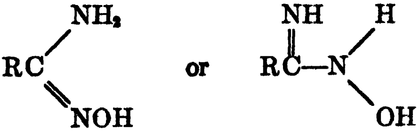


This product was different from the diethyl benzohydroxamate obtained by the reaction between benzohydroxamic acid and ethyl iodide (178).

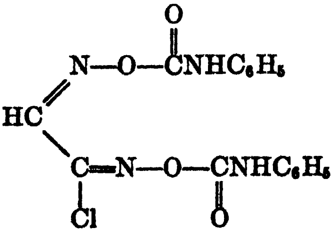
(*4*) *The reaction between ethyl ethoxycarbamate and an alkyl iodide in the presence of sodium alkoxide:* Jones and Neuffer (139) prepared $C_2H_5OCON(C_4H_9)OC_2H_5$ by the interaction of ethyl ethoxycarbamate and *sec*-butyl iodide in the presence of sodium ethoxide in alcoholic solution.

2. Monohydroxamyl halides

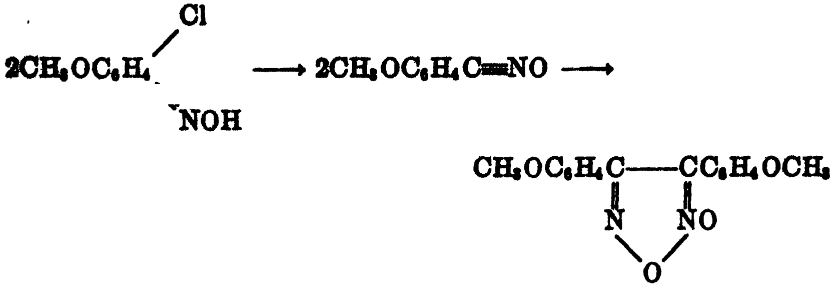
The monohydroxamyl halides, RCX=NOH, can be considered related to the monohydroxamic acids as acyl halides are related to carboxylic acids. The halogen atom in the monohydroxamyl halides was found to be much less reactive than the halogen in acyl halides. On hydrolysis, the monohydroxamyl halides yielded monohydroxamic acids, and with ammonia, they formed amidoximes (21, 308, 311, 313):



Phenyl isocyanate and formohydroxamyl chloride oxime, HC(=NOH)CCl=NOH, reacted (166) to yield



In dilute hydrochloric acid solution, acetohydroxamyl chloride and chlorine yielded 1,1-dichloro-1-nitrosoethane (225). Anisohydroxamyl chloride when treated with sodium carbonate yielded di(*p*-methoxyphenyl)furoxan (L) (151, 308, 311, 323).



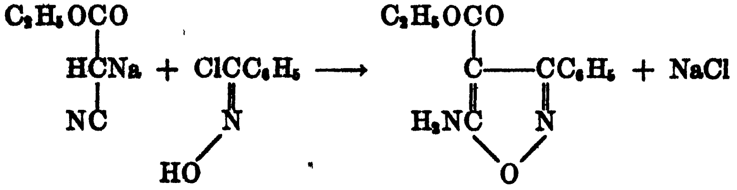
(40)

L

Di(*p*-methoxyphenyl)furoxan

From acetohydroxamyl chloride and silver nitrite there was obtained acetonitrolic acid; pyruvylohydroxamyl chloride and aqueous silver nitrate yielded silver fulminate (52, 225); silver fulminate and benzohydroxamyl chloride gave benzohydroxamyl fulminate, $C_6H_5C(=NOH)ON{=}C$ (328).

The monohydroxamyl halides were useful in the synthesis of isoxazole derivatives (242, 319).



(41)

Sodium azide and benzohydroxamyl chloride gave a tetrazole derivative (78), while hydrazine and acetohydroxamyl chloride yielded a triazole derivative (324).

Formohydroxamyl chloride has been the object of extensive investigations (50, 51, 198, 200, 201, 265, 293, 294, 327).

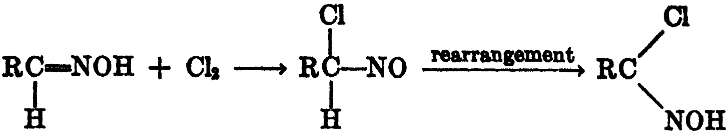
The monohydroxamyl halides gave the characteristic color test of monohydroxamic acids with ferric chloride.

It has been reported that benzohydroxamyl chloride, or an impurity intimately associated with it, caused an irritating skin rash (78).

Preparation

The monohydroxamyl halides have been prepared by the following methods:

(*1*) *The chlorination of an aldoxime:* The chlorination of an aldoxime to a monohydroxamyl chloride can be carried out in either chloroform or dilute hydrochloric acid solution (225, 308, 313, 322, 324). A transitory blue color formed during the reaction, owing to the presence of the intermediate chloronitroso derivative. Nitrosyl chloride and aldoximes also yielded monohydroxamyl chlorides (151, 248–250).



(42)

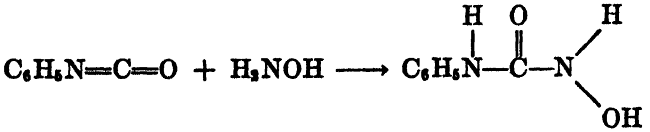
(*2*) *Miscellaneous methods of preparation:* Acetonitrolic acid (314), ethyl nitroacetate (278), or phenylnitromethane (202) with hydrochloric acid yielded, in each case, a monohydroxamyl chloride.

Several derivatives of the monohydroxamyl halides should be mentioned. Benzyl formohydroxamate and phosphorus pentachloride gave benzyl formohydroxamyl chloride (50). The reaction between *O*-ethylbenzamidoxime, hydrochloric acid, and sodium nitrite yielded ethyl benzohydroxamyl chloride (288, 292). Triphenylmethyl triphenylacetohydroxamyl chloride was prepared from triphenylmethyl chloride and silver fulminate (330).

3. Carbamylhydroxamic acids

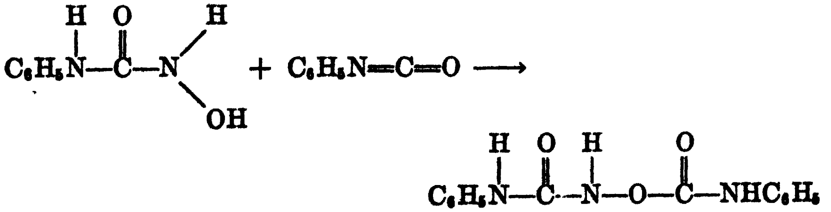
The carbamylhydroxamic acids are similar in many ways to the true hydroxamic acids. They are soluble in alkali and reduce Fehling's solution. With ferric chloride they give the intense violet color characteristic of the monohydroxamic acids (121).

Phenyl isocyanate is an acylating agent, and in its reactions it possesses a behavior very similar to that of the ketenes. Thus, with hydroxylamine there is a progressive substitution of hydrogen atoms in the order previously shown with the ketenes (44, 47, 48, 77, 121, 124, 150, 154).



LI

(43)

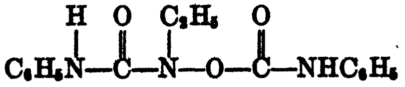


LII

(44)

The structure of LII, as well as of other hydroxyurea derivatives (70, 81, 154), has been discussed by Hurd (121).

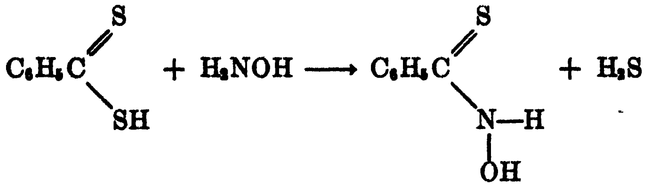
The reaction between *N*-ethylhydroxylamine and one equivalent of phenyl isocyanate gave ethyl phenylcarbamylhydroxamic acid, $C_6H_5NHCON(C_2H_5)OH$, which gave an intense color test with ferric chloride. With two equivalents of isocyanate the product was



$$C_6H_5\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-\overset{C_2H_5}{\overset{|}{N}}-O-\overset{O}{\overset{\|}{C}}-NHC_6H_5$$

4. Thiohydroxamic acids

A few of the sulfur analogs of the hydroxamic acids have been prepared. The reaction between dithiobenzoic acid, C_6H_5CSSH, and hydroxylamine yielded thiobenzohydroxamic acid (58).

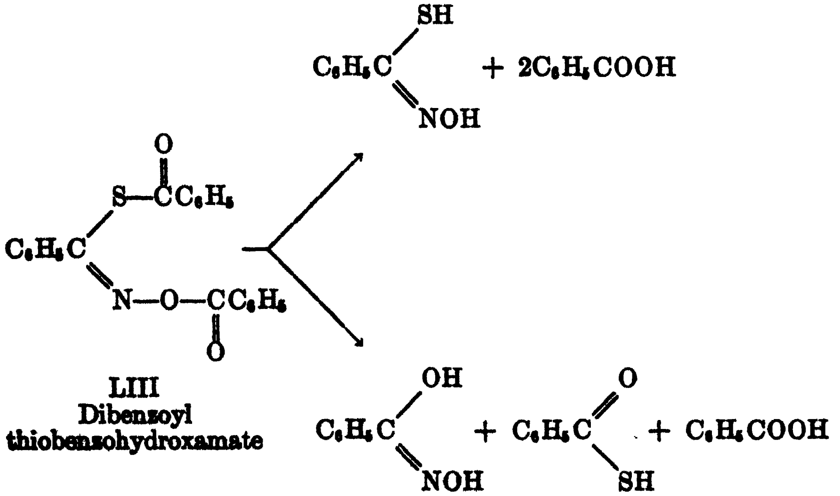


(45)

Dithiobenzoic acid

Thiobenzohydroxamic acid

Potassium thiobenzohydroxamate and benzyl chloride yielded benzyl thiobenzohydroxamate. Dibenzoyl thiobenzohydroxamate (LIII) was hydrolyzed in two ways by alcoholic potassium hydroxide:



(46)

LIII

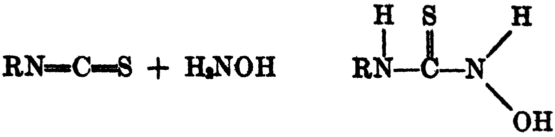
Dibenzoyl thiobenzohydroxamate

(47)

The principal reaction was that shown by equation 47.

Nef (198) found that silver fulminate and hydrogen sulfide gave thioformohydroxamic acid, $HC(SH)=NOH$.

The thiocarbamylhydroxamic acids were prepared by the reaction between hydroxylamine and isothiocyanates (48, 286).



$$RN{=}C{=}S + H_2NOH \qquad RNH{-}C({=}S){-}N(H)(OH) \qquad (48)$$

5. *Arylsulfonhydroxamic acids*

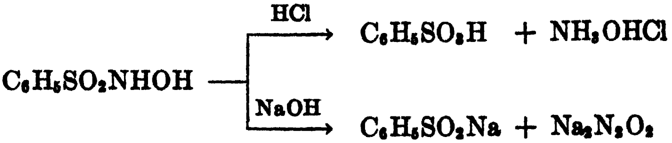
Piloty's Acid, benzenesulfonhydroxamic acid (224), was discussed previously (page 228) with regard to its utilization in the preparation of monohydroxamic acids from certain aldehydes. It was prepared by the reaction between benzenesulfonyl chloride and hydroxylamine (4, 14, 15, 224).

$$C_6H_5SO_2Cl + H_2NOH \qquad \underset{\text{Piloty's Acid}}{C_6H_5SO_2NHOH} \qquad (49)$$

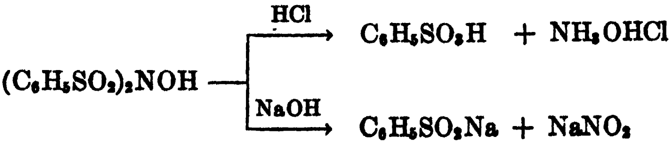
It gave the characteristic color test of monohydroxamic acids with ferric chloride (101).

The oxidation of benzenesulfonhydroxamic acid with ferric chloride or nitrous acid yielded $(C_6H_5SO_2)_2NOH$ (14, 156, 224). Fuming nitric acid gave the trisubstituted hydroxylamine derivative, $(C_6H_5SO_2)_3NO$.

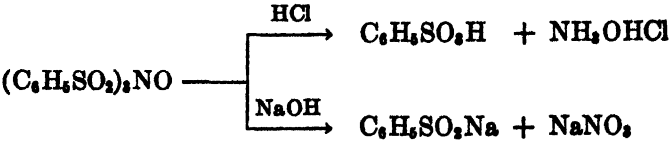
The behavior of these three derivatives when subjected to alkaline or acid hydrolysis is shown in the following equations:



$$C_6H_5SO_2NHOH \begin{cases} \xrightarrow{HCl} C_6H_5SO_3H + NH_3OHCl \\ \xrightarrow{NaOH} C_6H_5SO_2Na + Na_2N_2O_2 \end{cases} \qquad (50)$$



$$(C_6H_5SO_2)_2NOH \begin{cases} \xrightarrow{HCl} C_6H_5SO_3H + NH_3OHCl \\ \xrightarrow{NaOH} C_6H_5SO_2Na + NaNO_2 \end{cases} \qquad (51)$$



$$(C_6H_5SO_2)_3NO \begin{cases} \xrightarrow{HCl} C_6H_5SO_3H + NH_3OHCl \\ \xrightarrow{NaOH} C_6H_5SO_2Na + NaNO_2 \end{cases} \qquad (52)$$

Benzenesulfonhydroxamic acid and acetic anhydride, in excess, gave diacetyl benzenesulfonhydroxamate (224). It has been reported that benzenesulfonhydroxamic acid and a Grignard reagent subsequent to hydrolysis yielded benzenesulfonamide; if the reaction mixture prior to hydrolysis was treated with benzoyl chloride, the product obtained was $C_6H_5SO_2NHCOC_6H_5$ (215).

F. DIHYDROXAMIC ACIDS

The diacylated hydroxylamine derivatives are acidic. They give no color reaction with ferric chloride. The rearrangement of their alkali metal salts is their most characteristic reaction. They are not polymorphous. They can be titrated quantitatively with alkali, using thymol blue as the indicator (57, 247).

The dihydroxamic acids have been prepared by the following methods:

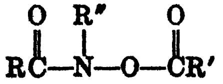
(1) The reaction between a salt of a monohydroxamic acid and an acyl halide: The finely pulverized salt, suspended in dioxane, was treated with the theoretical amount of acyl halide. The mixture was boiled for 5 min. and poured into water (247). Monohydroxamic acids and acid halides in the presence of an equivalent of alkali hydroxide, carbonate, or acetate, in various solvents, also yielded dihydroxamic acids (116, 140, 145, 170, 178).

(2) The reaction between an acid halide or acid anhydride and hydroxylamine: Hydroxylamine, or its addition product with chloral, reacted with acid anhydrides to yield dihydroxamic acids (97, 297). When two equivalents of benzoyl chloride and one equivalent of dry hydroxylammonium chloride were heated at 110°C. for 12 hr., benzoyl benzohydroxamate was obtained (108). The latter reaction may also be carried out in water (182, 305).

(3) Miscellaneous methods of preparation: Dihydroxamic acids were prepared by the reaction between acid halides and sodium *aci*-nitroalkanes (115, 132, 152, 199, 246). When the reaction was carried out in pyridine, the product was benzoyl benzohydroxamyl chloride (329). Phenylnitromethane, either on long standing (67) or on distillation at atmospheric pressure (107), gave benzoyl benzohydroxamate. Excellent yields of dihydroxamic acids were obtained from the reaction between a monohydroxamic acid and a ketene (124). The acid cleavage of alkyl acyl benzohydroxamates yielded dihydroxamic acids (182). The reaction between nitric oxide and the dipotassium salt of benzoin gave benzoyl benzohydroxamate as one of the products (262). Monohydroxamyl chlorides and silver salts of organic acids yielded dihydroxamic acids (313). Benzohydroxamic acid and potassium cyanide yielded benzoyl benzohydroxamate (188). The treatment of one equivalent of hydroxylamine with two equivalents of ethylmagnesium bromide, followed by benzoyl chloride, gave benzoyl benzohydroxamate.

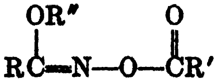
1. *Alkyl- and aryl-substituted dihydroxamic acids*

Compounds of the general formulas



$$\mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\text{—}\overset{\mathrm{R''}}{\overset{|}{\mathrm{N}}}\text{—O—}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R'}$$

or



$$\mathrm{R}\overset{\mathrm{OR''}}{\overset{|}{\mathrm{C}}}\text{=N—O—}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R'}$$

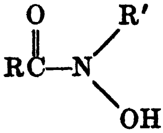
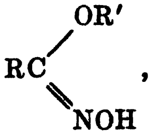
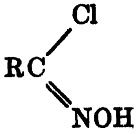
are polymorphous, existing in α- and β-modifications. The reaction between *N*-benzylhydroxylamine and benzoyl chloride led to benzyl benzoyl benzohydroxamate, possessing the single structure, $C_6H_5CON(C_6H_5)OCOC_6H_5$ (45, 46). On the other hand, the reaction between ethyl iodide and silver benzoyl benzohydroxamate gave ethyl benzoyl benzohydroxamate, capable of existing as either of the isomeric forms (72, 96, 178). Ethyl anisoyl benzohydroxamate, prepared by the reaction between anisoyl chloride and ethyl benzohydroxamic acid, also possessed two possible isomeric structures (222).

G. METAL SALTS OF THE MONO- AND DI-HYDROXAMIC ACIDS

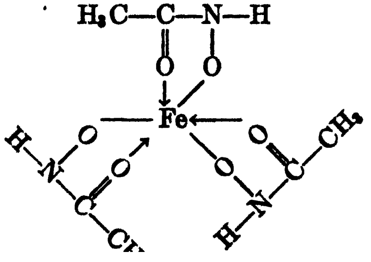
Salts of the monohydroxamic acids have been prepared with nearly all the elements of Groups I, II, and III of the Periodic Table, as well as zirconium, thorium, cobalt, nickel, and iron (109, 131, 136, 167, 169, 170, 219, 237, 310). Of these the iron, copper, cobalt, and nickel salts are of special interest. These compounds are colored and possess chelated structures.

Ferric acetohydroxamate may be isolated as deep red colored prisms by the reaction between acetohydroxamic acid and ferric ethoxide, in alcoholic solution (100). The salt is very soluble in water. It was found to be a better conductor of electricity than ferric acetylacetonate, gave no precipitate with potassium ferrocyanide, reacted only very slowly with ammonia to give ferric hydroxide, and was dissociated only by a high acid concentration. This stability differentiated these compounds from the colored enolates and phenolates (66, 74–76).

Since it is known that derivatives of the general formulas $RCONHOR'$ or $RC(OH){=}NOR'$ do not give color reactions with ferric chloride, while compounds of the structures


$RC(=O){-}N(R')OH$,

$RC(OR'){=}NOH$, and

$RC(Cl){=}NOH$

do, it is apparent that the $=NOH$ grouping is necessary for the formation of the coördination compound. Several possible structures have been proposed (LIV and LV) (66, 100, 122, 310).



LIV

$Fe[Fe(CH_3CONHO)_6]$

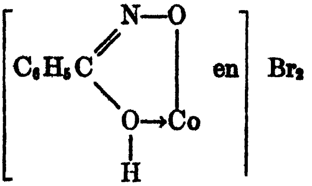
LV

Several basic ferric compounds, e.g., $(C_6H_5CONHO)_2FeOH$, have been described (71, 100).

The color test with ferric chloride is extremely sensitive. It will detect the presence of 2 γ of a carboxylic acid or acid anhydride (74–76).

The copper salts are green in color and very insoluble in water. Their principal use is in the isolation and purification of the monohydroxamic acids. Structurally they are similar to the ferric chelates (24, 71, 94, 163); they form basic and neutral salts. The neutral salts give no test for copper with potassium ferrocyanide, potassium thiocyanate, or hydrogen sulfide. The nickel-chelated monohydroxamates are similar to the copper salts.

Benzohydroxamic acid yielded a coördination compound with ethylenediamine and cobalt bromide (316).



The sodium and potassium salts of the dihydroxamic acids find application in studies on the Lossen rearrangement. The potassium salt undergoes reaction more readily than does the sodium salt. Both are very soluble in water and alcohol, and are prepared generally in absolute alcohol and precipitated with ether or dioxane (57, 140, 142, 247)

H. TRIACYLATED HYDROXYLAMINE COMPOUNDS

The triacylated hydroxylamine compounds were found to be polymorphous, existing in α-, β-, and γ-forms (161, 171, 173). In view of the methods utilized in their preparation, two isomeric structures were possible with these derivatives.

The monohydroxamic acids when treated with an excess of a ketene yielded triacylated hydroxylamine compounds in excellent yields (124); with acetic anhydride or acid halides, these derivatives were obtained only by prolonged treatment at elevated temperatures.

Other methods which have been utilized for the preparation of the triacylated hydroxylamine derivatives are:

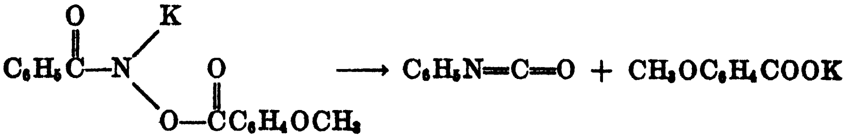
(*1*) *The reaction between a salt of a dihydroxamic acid and an acid halide:* Benzoyl chloride and silver benzoyl benzohydroxamate, after eighteen days at room temperature, gave dibenzoyl benzohydroxamate (171, 173).

(*2*) *The reaction between hydroxylamine and an acid chloride:* Dibenzoyl benzohydroxamate was formed, along with benzoyl benzohydroxamate and benzohydroxamic acid, by the interaction of benzoyl chloride and hydroxylamine (169).

(*3*) *The reaction between sodium aci-nitroalkanes and acid halides:* The reaction between sodium *aci*-nitroethane and benzoyl chloride yielded dibenzoyl acetohydroxamate (132, 199).

II. THE LOSSEN REARRANGEMENT

The Lossen rearrangement, in its broadest interpretation, occurs as a result of the thermal decomposition of hydroxamic acids or their derivatives. As a consequence, a group attached to carbon originally is found joined to nitrogen in the final product. The rearrangement was first observed by Lossen (169), apparently by accident, when he heated benzoyl benzohydroxamate above its melting point and obtained a lachrymatory substance (phenyl isocyanate). Soon afterward he reported that potassium anisoyl benzohydroxamate in boiling water readily gave diphenylurea, potassium anisoate, and carbon dioxide (170–172).



$$C_6H_5C(=O)-N(K)-O-C(=O)C_6H_4OCH_3 \longrightarrow C_6H_5N{=}C{=}O + CH_3OC_6H_4COOK \qquad (53)$$

$$C_6H_5N{=}C{=}O + H_2O \longrightarrow C_6H_5NH_2 + CO_2$$

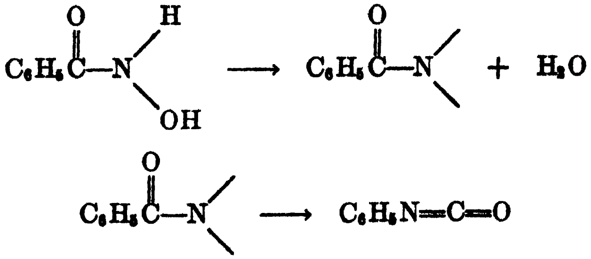
$$C_6H_5NH_2 + C_6H_5N{=}C{=}O \longrightarrow (C_6H_5NH)_2CO$$

The Lossen rearrangement is now taken to mean the latter type of reaction, although a variety of hydroxamic acid derivatives when subjected to destructive distillation undergo this change (89, 96, 121a, 173, 222, 223, 290). Rearrangement has been effected also by heating hydroxamic acids and their derivatives with thionyl chloride (189), acetic anhydride (203), and phosphorus pentoxide (33, 146).

A. Mechanism of the Lossen rearrangement

The Lossen rearrangement possesses an inherent similarity to the Hofmann, Curtius, and Beckmann rearrangements (49, 53, 57, 105, 247, 273, 280–283, 302–304). There has been a tendency to refer to them collectively as Beckmann rearrangements, although no great purpose can be accomplished by such a classification (53).

Although Lossen (175) was aware of the similarity between his rearrangement and the Hofmann rearrangement, he was apparently free of curiosity concerning its mechanism. Tiemann (290), in attempting to explain the formation of carbon dioxide and aniline by the destructive distillation of benzohydroxamic acid, proposed that the reaction proceeded through an intermediate univalent nitrogen derivative which rearranged to an isocyanate.

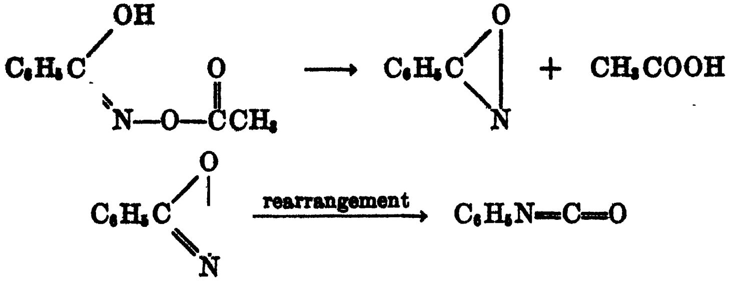


$$C_6H_5C(=O)-N(H)-OH \longrightarrow C_6H_5C(=O)-N< + H_2O$$

$$C_6H_5C(=O)-N< \longrightarrow C_6H_5N{=}C{=}O \qquad (54)$$

$$C_6H_5N{=}C{=}O + H_2O \longrightarrow C_6H_5NH_2 + CO_2$$

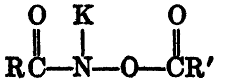
As an alternative to the univalent nitrogen compound, Hantzsch (99) proposed a cyclic intermediate.



(55)

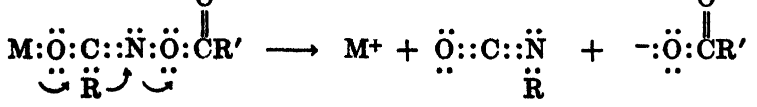
The hypothesis that a univalent nitrogen derivative was the intermediate in the Lossen rearrangement was largely developed by Jones and his students on the basis of the pioneer work of Stieglitz (53, 280–283) and Schroeter (53, 267). Jones considered this mechanism the most satisfactory explanation for the rearrangement, and indirectly indicated the structure of the hydroxamic acids as RCONHOH (133, 144–146). Gastaldi (84, 87, 89, 93) used this mechanism to explain the formation of 1,2,4-triazole derivatives from the arylhydrazones of pyruvylohydroxamic acid.

Hauser and his students (57, 105, 247) showed that the rearrangement velocity in a series of compounds of the type,



$$R\overset{O}{\overset{\|}{C}}-\overset{K}{\overset{|}{N}}-O-\overset{O}{\overset{\|}{C}}R'$$

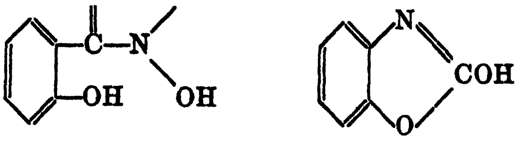
was directly related to the ionization constant of the acid, R′COOH, when R was held the same, or indirectly related to the ionization constant of RCOOH, if R′ was held constant. Baker (23) previously noted this same generalization, i.e., the facility with which the Lossen rearrangement occurred with the acylated monohydroxamic acids increased with the increasing anionic stability of the anionizing group. This was essentially the requirement for a pinacol-type rearrangement.



$$M:\overset{..}{\underset{..}{O}}:\underset{R}{C}::\overset{..}{N}:\overset{..}{\underset{..}{O}}:\overset{O}{\overset{\|}{C}}R' \longrightarrow M^+ + \overset{..}{\underset{..}{O}}::C::\overset{..}{\underset{\underset{R}{..}}{N}} + {}^-:\overset{..}{\underset{..}{O}}:\overset{O}{\overset{\|}{C}}R' \quad (56)$$

According to this mechanism, there occurred first a depletion of electrons around the nitrogen atom, necessitating the migration of R with its pair of electrons from the adjacent carbon atom. The tendency of M to part from, and of $O\overset{O}{\overset{\|}{C}}R'$ to retain, bond electrons during the formation of the ions M^+ and $^-:\overset{..}{\underset{..}{O}}:\overset{O}{\overset{\|}{C}}R'$ furnished the driving force for the reaction.

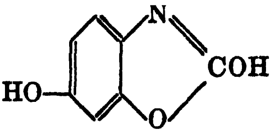
The recent work of Scott and his students (269–272), based on the early work of Marquis (189), indicated that isocyanates may not always be intermediates in the Lossen rearrangement. Marquis found that salicylohydroxamic acid and thionyl chloride gave oxycarbanil (LVI) instead of *o*-hydroxyphenyl isocyanate.



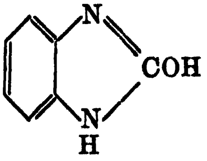
LVI
Oxycarbanil

(57)

Scott and Mote (271) also obtained oxycarbanil from potassium benzoyl salicylohydroxamate. In the same way, potassium acetyl 2,4-dihydroxybenzohydroxamate gave 4-hydroxycarbanil (LVII) (270), and potassium benzoyl-*N*-benzoylanthranilohydroxamate gave 2-oxybenzimidazole (LVIII) (272).

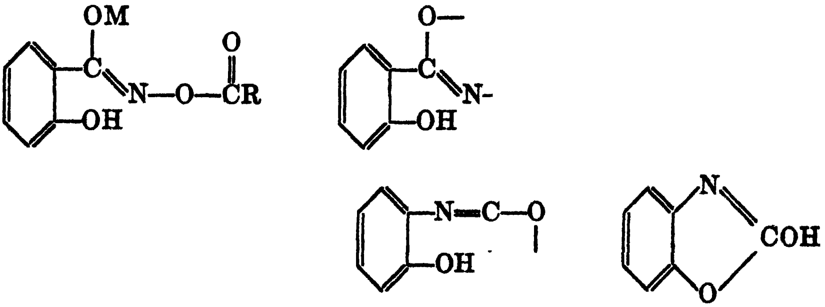


LVII
4-Hydroxycarbanil



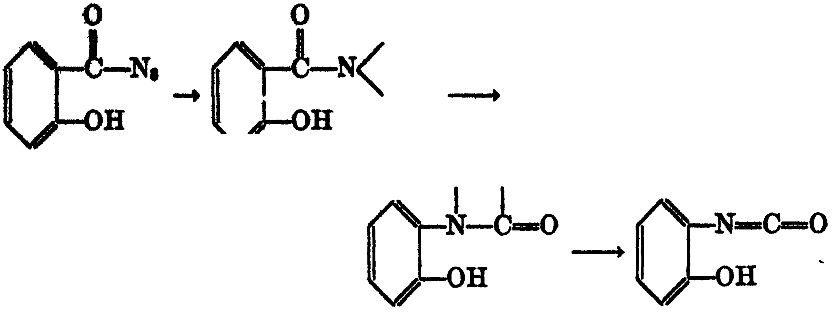
LVIII
2-Oxybenzimidazole

Scott and Kearse (270) preferred a mechanism which involved the hydroxyoxime structure of the metal salt of the acylated salicylohydroxamate, and was not based on the formation of an isocyanate.



(58)

In the Curtius rearrangement of the azide of salicylic acid there was formed a univalent nitrogen derivative capable of rearranging to an isocyanate.



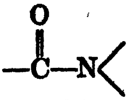
(59)

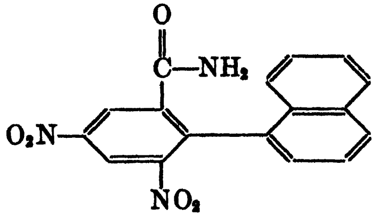
A significant part of the mechanism of the Lossen rearrangement is concerned with the shift of the R group from carbon to nitrogen. Since a carbon–carbon linkage is severed in this process, it appeared reasonable to assume that the R group must exist at least momentarily as a free radical. Jones and Hurd (136) made a comparative study of the rearrangement of the potassium salts of the benzoyl phenyl-, diphenyl-, and triphenyl-acetohydroxamates and found that the ease of rearrangement was greatest with the triphenyl derivative and least with the phenyl derivative. As a consequence of these observations, it appeared that the relative ease of rearrangement was dependent upon the tendency for the radical R in the univalent nitrogen derivative to exist as a free radical.

Further evidence for this thesis lay in the comparative stability of the potassium salts of benzoyl *o*- and *p*-benzhydrylbenzohydroxamate which were isomeric with the triphenylacetohydroxamic acid derivative (143); in the ready rearrangement of potassium benzoyl dibenzylacetohydroxamate when compared with the corresponding monobenzyl compound (144); in the rearrangement of the sodium salts of acylated diphenylcarbamylhydroxamates and the absence of any rearrangement with the phenylcarbamylhydroxamates (121); and in the ease of rearrangement of the salts of the acylated diphenyl-*p*-tolylacetohydroxamates (123).

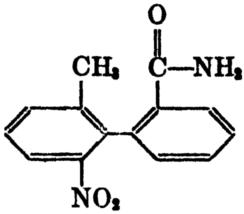
In order to study this hypothesis critically, Jones and Wallis (147) and Wallis and Dripps (301) investigated the rearrangement of optically active hydroxamic acid derivatives. The latter subjected potassium benzoyl *d*-benzylmethylacetohydroxamate to rearrangement and obtained an optically active isocyanate which when hydrolyzed yielded an optically active amine. There was sufficient evidence to indicate that partial racemization had not occurred during the rearrangement.

Jones and Wallis (147) suggested that optical stability could be maintained by the radical if it were to exist as a positive (or negative) ion, or, if the rearranging group did not exist in the free state, but was so under the influence of the univalent nitrogen atom that, when cleavage occurred, a change in the configuration of the asymmetric carbon atom was prevented. This influence was presumed to be that of partial valences.

In a related study of the Hofmann rearrangement of *d*-3,5-dinitro-6-(α-naphthyl)benzamide (LIX), Wallis and Moyer (302) found that no racemization had occurred. If a positive or negative radical had existed, the blocking effect of the  $-\overset{\overset{\displaystyle O}{\|}}{C}-N\langle$ would have been removed and free rotation about the axial bond would have been possible. Since not even partial racemization had occurred, they concluded that no free radicals had formed and suggested the existence of partial valences as an explanation. Bell (49) showed that the optically active 6-nitro-2-methyldiphenyl-2′-carboxamide (LX) when subjected to rearrangement also gave no evidence of racemization in the product.



LIX

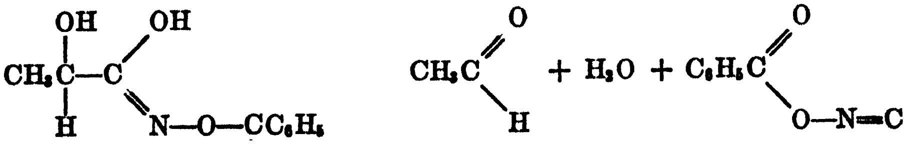


LX

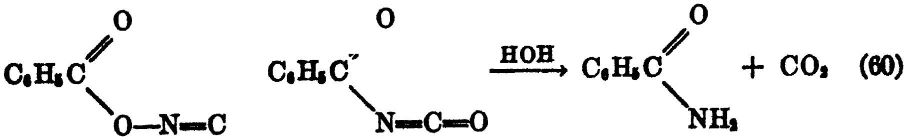
Bell suggested as an alternative explanation the possibility that the radical existed for a short time compared to the time required for rotation of the two aromatic nuclei.

B. Anomalous behavior in the Lossen rearrangement

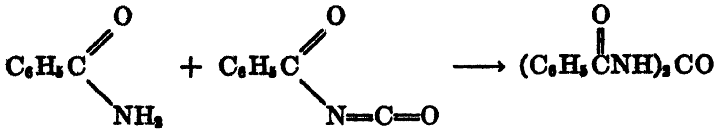
The hydroxamic acids and their derivatives when subjected to the conditions necessary for the Lossen rearrangement are known to give other anomalous reactions. For example, heating a mixture of benzoyl lactohydroxamate (LXI) and water yielded acetaldehyde, dibenzoylurea, carbon dioxide, ammonia, and ethyl alcohol. The formation of several of these products can be attributed to a dissociation of the hydroxyoxime structure of LXI into acetaldehyde and benzoylfulminate (LXII), which could then rearrange to benzoyl isocyanate (LXIII) (140).



LXI LXII

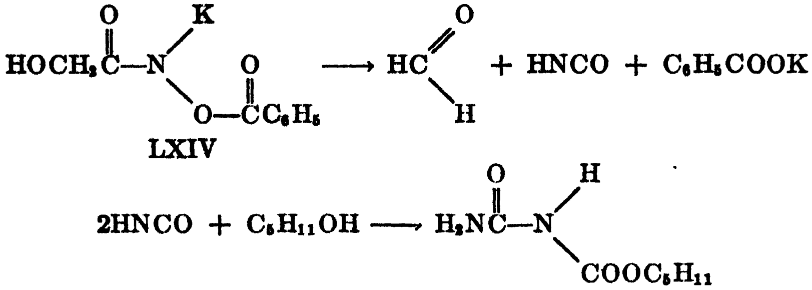


LXIII (60)



Under similar conditions benzoyl mandelohydroxamate gave benzaldehyde as one of the products.

Formaldehyde and isoamyl allophanate were obtained in a related reaction between potassium benzoyl glycolohydroxamate (LXIV) and isoamyl alcohol. The intermediate dissociation products were presumed to be formaldehyde and cyanic acid (142).



LXIV

(61)

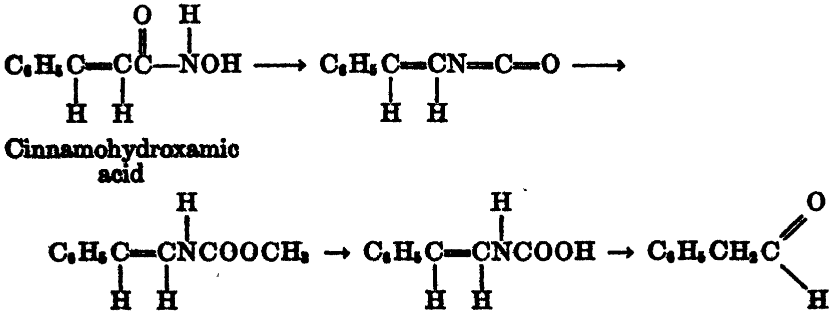
Isoamyl allophanate

It appeared that compounds which have an OH group in the α-position yield an aldehyde or ketone and cyanic acid when subjected to the Lossen rearrangement. If the rearrangement occurred in water, the products were urea or carbon dioxide and ammonia, while in alcohol the product was an allophanate.

In this connection it was interesting to note that dry potassium benzoyl methoxyacetohydroxamate, heated at 115–120°C., yielded potassium benzoate and methoxymethyl isocyanate (142).

Potassium benzoyl cinnamohydroxamate underwent no rearrangement in boiling water; it reacted in alcohol to yield ethyl styrylcarbamate (137). Warming either oleo- or elaido-hydroxamic acid with an excess of acetic anhydride led to a mixture of *cis*- and *trans*-heptadecylenyl isocyanates. Apparently rearrangement of the double bond had occurred (203).

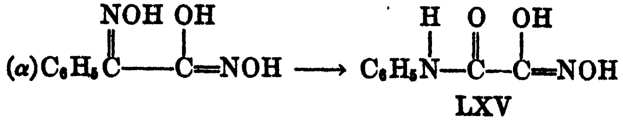
The Lossen rearrangement was used to prepare phenylacetaldehyde from cinnamohydroxamic acid (284) and epicamphor from bornylene-3-hydroxamic acid (56).



Cinnamohydroxamic acid

(62)

An interesting reaction was reported by Gastaldi (92). He treated α-benzoylformohydroxamic acid oxime with phosphorus pentachloride in dry ether and obtained phenylcarbamylformohydroxamic acid (LXV). This was an example of a Beckmann rearrangement which proceeded without disturbing the hydroxamic acid.



$$(\alpha)C_6H_5\overset{NOH}{\overset{\|}{C}}-\overset{OH}{\overset{|}{C}}{=}NOH \longrightarrow \underset{LXV}{C_6H_5\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{|}{C}}{=}NOH} \qquad (63)$$

The carbamylhydroxamic (121, 126), thiocarbamylhydroxamic (286), arylsulfonhydroxamic (224, 320), and thiobenzohydroxamic (58) acids and their derivatives did not undergo the Lossen rearrangement.

C. Temperature and alkalinity as factors in the Lossen rearrangement

Mohr (196) found that the quantity of alkali present during the rearrangement of dihydroxamic acids determined the relative amounts of urea and aniline formed. The neutral potassium or sodium salt in dilute aqueous solution was completely decomposed at 70°C. in 2 hr. and gave principally diphenylurea and some aniline. An excess of dilute alkali (0.1 *N*) yielded chiefly aniline. With increasing dilution of the alkali, the ratio of aniline to diphenylurea was increased.

Dougherty and Jones (68) made rate studies on the rearrangement of benzoyl benzohydroxamate in the presence of two equivalents of potassium hydroxide at 25°C. At this temperature reaction was incomplete after approximately 100 hr. They detected the presence of aniline and benzohydroxamic acid almost immediately; the odor of phenyl isocyanide was evident after 15 hr. Phenyl isocyanate was present in small amounts. After 25 hr. a precipitate of diphenylurea formed which increased as the reaction progressed. No satisfactory rate constants were obtained for the first 25 hr. during which 25 per cent of the reaction occurred; with the formation of diphenylurea, constants for a first-order reaction were obtained. The variation in the constants for the first one-quarter of the reaction was attributed to the presence of free alkali. This excess alkali hydrolyzed some of the potassium benzoyl benzohydroxamate to potassium benzohydroxamate and potassium benzoate; it also hydrolyzed phenyl isocyanate to aniline. The rôle of the alkali became more insignificant, and the reaction rate fairly constant as a result of the reaction of phenyl isocyanate with aniline, indicated by the appearance of diphenylurea.

Renfrow and Hauser (247) eliminated these difficulties to a large extent by measuring the rates of reaction of the potassium salts of the dihydroxamic acids in 0.1 *N* ammonia solution. Ammonia reacted with aryl isocyanates to form soluble arylureas, but the hydroxyl-ion concentration was insufficient to cause appreciable hydrolysis of the dihydroxamic acids.

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POLYHYDRIC ALCOHOL ESTERS OF FATTY ACIDS

THEIR PREPARATION, PROPERTIES, AND USES

H. A. GOLDSMITH

Glyco Products Co., Inc., Brooklyn, New York

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The methods of preparation, the physical and chemical data, and the industrial applications of the higher fatty acid esters of polyhydric alcohols and of polyhydroxy ethers are reviewed. Triglycerides are not included.

In the course of studies concerning the polyhydric alcohol esters of the higher fatty acids, it becomes apparent that there is a need for a complete and systematic survey of all facts recorded in the literature about the preparation, properties, and uses of this group of substances. While much work has been done, much information has been omitted, and there are many contradictory statements. Reviews thus far published have surveyed only part of the subject (124, 223, 382, 400, 452); this literature review is meant to fill the gap.

To clarify the scope of this review, polyhydric alcohol esters of higher fatty acids shall be defined to include the esters of the higher fatty acids (i.e., straight-chain monocarboxylic acids, from C_8 up) with the polyhydric alcohols (i.e., diols, triols, tetrols, pentitols, hexitols), the polyhydroxy ethers (i.e., the polyalkylene glycols, polyglycerols, polymerized pentaerythritol or hexitols, hydroxyalkyl ethers of polyhydric alcohols), and the simpler carbohydrates (mono-, di- and tri-saccharides).

While definitely within this group, synthetic and natural triglycerides had to be excluded as they have been amply covered by the literature on fats and oils.

Polyhydric alcohol esters of higher fatty acids are not a new group of chemicals. The first glycerides were prepared as early as 1853 (38), erythritol, dulcitol, mannitol, and glucose esters in 1855 (40), and the first glycol esters in 1859 (563). Yet the first patent on glyceride manufacture was granted only in 1907 (546), and another fifteen years passed before industry began to take an interest in the polyhydric alcohol esters. Today, however, a considerable patent literature is witness to their growing industrial importance.

Two basic types of polyhydric alcohol esters can be distinguished: (*1*) those in which all alcoholic hydroxyl groups have been esterified; (*2*) those in which only part of them have been esterified. They will be referred to as the completely and the partially esterified polyhydric alcohols.

There are no distinct borderlines between these two groups. Similar methods of preparation, similar properties, and similar uses make it very difficult to consider them separately. However, the partially esterified polyhydric alcohols have received much more attention because of certain surface-modifying properties inherent in them. While both groups have much in common with the glyceride fats, it will be seen that considerable modification of properties is possible when triglycerides are replaced by mono- or di-glycerides, or by esters of other polyhydric alcohols.

It is possible to modify the polyhydric alcohol esters further, chiefly for use as surface-active agents, by the introduction of sulfuric, sulfonic, sulfoacetic, phosphoric, boric acid and other radicals. Such materials, though important, are beyond the scope of this survey.

I. PREPARATION OF THE POLYHYDRIC ALCOHOL ESTERS OF HIGHER FATTY ACIDS

All polyhydric alcohol esters can, in general, be prepared by the same basic methods which were originally worked out for the preparation of the glycerides. These basic methods are: (*1*) direct esterification of hydroxyl groups with fatty acids or anhydrides, with or without a dehydrating agent; (*2*) esterification by means of fatty acid halides with removal of hydrogen halide; (*3*) reësterification; (*4*) reaction of halogen groups with fatty acid salts, with formation of metal halide; (*5*) hydrolysis; (*6*) addition of alkylene oxides to compounds containing hydroxyl or carboxyl groups. Etherification, by dehydration, may accompany esterification or reësterification.

For greater clarity, however, the methods have been arranged according to the starting materials employed:

A. Polyhydric alcohols.
B. Fully esterified polyhydric alcohols.
C. Anhydro derivatives of polyhydric alcohols.
D. Substituted derivatives of polyhydric alcohols.
E. "Protected" derivatives of polyhydric alcohols.
F. Compounds related to polyhydric alcohols.

A. PREPARATION FROM POLYHYDRIC ALCOHOLS

A. Direct esterification

The direct reaction of polyhydric alcohols with fatty acids is the oldest recorded, and probably the simplest, way in which to make polyhydric alcohol esters. Its advantages are simplicity of equipment, operation, and control, and the ready commercial availability of raw materials. However, it has several disadvantages. Even though some esterification occurs at ordinary temperatures, if given enough time (39), its progress is slow at low temperatures and long heating or high temperatures are required to carry the reaction to completion. It cannot be used, therefore, when there is danger of undesirable chemical changes (polymerization, dehydration, resinification, or charring) in a reactant under these conditions. The greatest disadvantage of the method, however, is observed when polyhydric alcohols are to be only partially esterified. In such cases, mixtures of more and less completely esterified polyhydric alcohols form, even if a large excess of the alcohol is used. Most polyhydric alcohols are not, or are only poorly, miscible with the fatty acid, even at elevated temperature, while their ester products are. Thus, the fatty acids react with the ester products rather than with the polyhydric alcohols themselves, yielding more highly esterified products than intended. It may be stated at this point that various improvements in the method have been made which have wholly or partially eliminated its disadvantages. Thus, by the use of catalysts, mutual solvents, carrier solvents and traps, improved agitation, and the passage of currents of inert gas, better and more homogeneous products may now be obtained in shorter time and with greater yield.

Unaided direct esterification of polyhydric alcohols, like other esterifications, is increased in speed when the temperature is raised. The proportion of the reactants, the speed of moisture removal, the size of the batch, and the use and efficiency of agitation also strongly influence its progress. The more complex polyhydric alcohols seem to esterify more slowly than the less complex ones, but the data appearing in the literature allow no reliable conclusions. The esterifications were often not carried to completion, or were stopped at an indefinite point. Thus, reactions carried out in sealed tubes can be expected to have reached an equilibrium point, but not completion. Hence, data on reaction time are approximations at best. These esterifications have usually been carried out at 150° to 250°C., and preferably as high as the boiling or decomposition points of the reactants allowed (tables 1, 2, and 3).

TABLE 1

Esterification of glycols and ether-glycols with fatty acids, without catalyst

GLYCOL	TIME	REACTION TEMPERATURE	REACTION CONDITIONS	REFERENCES
	hours	°C.		
Ethylene glycol.........		100	Sealed tube	(518)
		150	Special stirring, CO_2	(370)
	4–7	170–210	Open vessel	(101, 158, 473, 474)
			Reflux or partial reflux	(407, 482, 483)
	5–11	200–205	Special stirring, CO_2	(73, 424)
		Above 210		(287, 353)
1,2-Propylene glycol....	7–8	157–167	Open vessel	(262)
	6–8	210–230	CO_2	(353)
1,3-Propylene glycol....		170–180	Open vessel	(262)
Diethylene glycol.......	2½	180–210	CO_2	(158)
	6–8	210–230	CO_2	(353)
Triethylene glycol	6	180–210	CO_2	(158)
Polyethylene glycol.....		130		(275, 302, 488)
		200		(131)

In the case of mono- and di-glycerides, the course of reaction has been more carefully studied: when 1 mole of glycerol and 1 mole of fatty acid (oleic, palmitic, stearic) are reacted at 215–220°C. under a pressure of 30–40 mm. of mercury, the

TABLE 2

Esterification of glycerol with fatty acids, without catalyst

TIME	REACTION TEMPERATURE	REACTION CONDITIONS	REFERENCES
hours	°C.		
114	100	Sealed tube	(38, 39)
114	100	Open retort, collecting water of reaction	(97)
5–8	160–180	Sealed tube	(42, 379, 441, 545)
4–45	150–160	Open vessel, CO_2	(259, 370)
6–52	200–220	Sealed tube	(38, 39, 42, 253, 264, 379)
2–50	170–220	Open vessel, inert gas; also in retort, collecting water of reaction	(73, 87, 97, 157, 187, 241, 249, 250, 325a, 335, 370, 537)
4–8	170–200	Vacuum	(28, 187, 352, 441, 546)
	230–250	Autoclave	(189, 481)
½–5	220–260	Open vessel, inert gas	(87, 155, 156, 157, 287, 335, 370, 453)
5–40	200–250	Vacuum	(28, 68, 548)
7–10	250–275	Sealed tube	(39, 364)
		Partial reflux, allowing elimination of water	(407)
3–6	280–290	Vacuum	(189, 390)

TABLE 3

Esterification of higher polyhydric alcohols with fatty acids, without catalyst

POLYHYDRIC ALCOHOL	TIME	REACTION TEMPERATURE	REACTION CONDITIONS	REFERENCES
	hours	°C.		
Polyglycerol		250	Sealed tube	(133, 264)
Glycerol trihydroxyethyl ether	2	175		(274, 288, 308, 487)
	10	205		(274, 288, 308, 487)
Erythritol		200–250	Sealed tube	(40, 44, 375)
		200–205	Open vessel	(477)
Pentaerythritol	6	180, 200, 220, 240		(56)
	6–10	200–220		(53)
		220–235		(87)
Hexitols	15–20	200–260	Sealed tube	(40, 41, 44)
	3–10	200–260	Open vessel or vacuum	(53, 87, 273, 286, 288, 370, 418)
Hexitol hydroxyethyl ethers	3–10	170–210		(274, 288, 487)
Glucose, sucrose	50–60	120	Sealed tube; poor yields	(40, 43)
Trehalose		180	Sealed tube	(43)

bulk of fatty acid disappears in about 2 hr., but an excess of unreacted glycerol remains. Monoesters form initially, but after the first half hour diesters prevail. If the reaction is continued after all fatty acid has reacted, the amount of monoglycerides again increases and the unreacted glycerol is used up (28).

At 160–180°C., 50–70 per cent of the fatty acid is esterified in about 4 hr. Depending upon the ratio of glycerol (1–10 moles) to fatty acid (1 mole), however, only 32–46 per cent of the esters formed are monoglycerides (259).

A mixture of monoglycerides and diglycerides forms when 0.8–1.4 moles of glycerol are reacted with 1 mole of fatty acid. Esterification was found almost complete after 15–20 hr. at 170–180°C., and after 3 hr. at 230–240°C. At lower temperatures, less mono- and di-glycerides were formed than at higher temperatures. If lauric or oleic acid was used, chiefly mono- and di-glycerides were formed, but with stearic acid di- and tri-glycerides prevailed (335).

No detailed study seems to have been made on any of the other polyhydric alcohols, with the possible exception of a study on pentaerythritol (56) and on erythritol esters (477).

Many catalysts speed up the esterification of polyhydric alcohols. Acidic, neutral, and alkaline catalysts have been suggested, but no systematic investigation of the comparative merits of these catalysts has ever been recorded.

Dry hydrogen chloride gas has been suggested for the esterification of glycols (128, 139, 557), polyglycols (199, 339), glycerol and polyglycerols (38, 128, 139, 187), pentaerythritol, hexitols, and sugars (53, 139, 294) at temperatures ranging from 100° to 260°C. However, products containing chlorine may result from its use (38, 39, 53, 187).

The esterification of glycols (94, 199, 339, 432, 439, 557), glycerol and polyglycerol (39, 131, 147, 432, 439, 457), pentaerythritol, hexitols, and sugars (53, 147, 274, 288, 432, 487), and hydroxyalkyl ethers of glycerol or hexitol (274, 288, 487) may be catalyzed by sulfuric acid. However, sulfuric acid readily affects the color and purity of most chemicals coming in contact with it (39, 53), and cannot be used indiscriminately.

Phosphoric acid has also been used repeatedly (39, 199, 274, 288, 459). Boric acid is suggested for the higher polyhydric alcohols and their hydroxyalkyl ethers (274, 288, 294, 304, 487); anhydrous sulfur dioxide gives good color to reaction products of glycerol, but at the same time it isomerizes oleic acid and probably other unsaturated acids (187).

Acid salts, such as zinc chloride, calcium chloride, or copper sulfate, as well as certain phosphates, have been suggested as catalysts (33, 53, 139, 154, 271, 294, 557). Zinc chloride, particularly, is described as an ingredient of certain solid surface catalysts used at high temperatures, where at least one of the reactants is present in vaporized or finely suspended (mist) form.

A group of catalysts widely used for the esterification of polyhydric alcohols is that of organic sulfonic acids, such as the sulfonic acids of benzene, toluene, naphthalene, or camphor, and the so-called Twitchell reagents (table 4). They possess the effectiveness of sulfuric acid, but do not have its carbonizing action, and may be used in very small quantities. However, while increasing the ester yield, the presence of such sulfonic acids in the preparation of monoglycerides will lower the monoglyceride yield (259). This, of course, may be true for all catalysts.

Acetyl chloride has recently been suggested as a catalyst for the esterification of glycol in the cold (183).

The finely powdered metals, such as zinc, tin, iron, manganese, platinum, antimony, bismuth, lead, and titanium, or combinations of metals such as zinc–copper or zinc–silver are used as catalysts, either in suspension in the reacting medium or precipitated on a porous base. Shortened reaction time and light-colored products are said to be thus obtained in the esterification of glycols (297, 386), glycerol (205, 297, 298, 480), polyglycerol (491, 495), and erythritol (518).

TABLE 4

Esterification of polyhydric alcohols with higher fatty acids, using sulfonic acid catalysts

POLYHYDRIC ALCOHOL	TIME	REACTION TEMPERATURE	CATALYST (SULFONIC ACID)	REFERENCES
	hours	°C.		
Glycol............	4–5	Benzene reflux	Aromatic	(103)
	4	120, 140, 180	Camphor	(259)
			Naphthalene	(329)
			Twitchell reagent	(147, 432)
			Alkyl or aryl	(316)
		150	Twitchell reagent	(258, 384)
Glycerol..........	4, 6	100	Twitchell reagent	(139, 321, 544)
	4–5	Benzene reflux	Aromatic	(57)
	¼–4	120–180	Camphor	(89, 259)
	1	140	*p*-Toluene	(54, 57)
			Naphthalene	(329)
	4	160–180	Naphthalene and camphor	(260, 314)
			Twitchell reagent	(147, 432)
			Alkyl or aryl	(316)
	3	Dioxane reflux	Twitchell reagent	(457)
Others............			Twitchell reagent	(16, 147)

Amphoteric metallic oxides, such as titanium dioxide (93), bismuth oxide (298), and tin or aluminum oxides (267, 272, 300), have been mentioned as catalysts. However, basic oxides, basic salts, and particularly alcoholates and soaps have found much wider acceptance for this purpose (table 5). There seems to be no evidence as to whether or not this basic group yields more valuable catalysts than the acid group. For many commercial uses a soap content of a polyhydric alcohol ester is not undesirable; thus there is no objection to the use of alkaline catalysts.

In the preparation of partial esters of polyhydric alcohols, a large excess of polyhydric alcohol is normally necessary to produce a preponderance of the desired partial esters, such as monoesters, over the more highly esterified prod-

TABLE 5

Esterification of polyhydric alcohols with higher fatty acids, using basic catalysts

POLYHYDRIC ALCOHOL	TIME	REACTION TEMPERATURE	CATALYST	REFERENCES
	hours	°C.		
Glycol	2	200	Sodium glycerophosphate	(31, 32)
		230	Zinc, tin, magnesium oxides	(300)
	2–3	180–200	Tin oleate	(254, 270, 284, 296, 299)
	½	230	Metallic soap	(271)
Polyglycols	Few minutes	Reflux	Sodium metal	(540)
	2	200	Sodium glycerophosphate	(32)
Glycerol	1–5	200–220	Sodium hydroxide; calcium, sodium, potassium glyceroxides	(100, 203)
		100–200	Sodium glyceroxide (instead of glycerol)	(99)
	3	275	Potassium soap	(303)
	10	180	Potassium soap	(373)
		170–210	Magnesium oxide	(298)
		180–250	Zinc, magnesium oxides	(272, 300)
	4–5	170–250	Tin, zinc, aluminum, and magnesium soaps	(267, 281, 293)
	2–7	180–200	Tin oleate	(254, 270, 284, 296, 299)
	½	230	Metal soaps	(271)
Polyglycerols		250–300	Potassium hydroxide	(461)
	1–1½ 2¼ 16	220–230 205 190–200	Alkaline catalyst from glycerol polymerization	(160, 161, 228, 236, 238, 240, 241, 250)
	4–5	260	Sodium acetate	(491, 495)
	16	190–200	Sodium glyceroxide	(228)
			Magnesium oxide, trisodium phosphate	(415)
Pentaerythritol	5	220	Sodium hydroxide	(203)
	1–4	240	Lead, calcium, zinc, sodium oxide	(14, 143)
	3½	190	Lead oxide	(504)
Mannitol	8½	180	Lead oxide	(504)
	5	220	Sodium hydroxide	(203)
Quebrachitol	8	235–245	Magnesium oxide	(315)

ucts; pure materials are not obtained even then, and the purification takes time and is not always successful. The use of mutual solvents, such as the phenols (69, 89, 147, 259, 260, 314, 432) or ethers such as dioxane (457), permits using only a slight excess of polyhydric alcohol, yet gives a higher percentage of partial esters.

To esterify polyhydric alcohols at lower temperatures, carrier solvents may be used. Their function is to remove water by maintaining the reaction mixture at its boiling point. If these solvents are immiscible with water, the azeotropic distillate may be condensed into a Bidwell–Sterling tube, where the water may be separated from it and the carrier may be returned into the reaction vessel, allowing the continuous use of a small amount of solvent. Toluene, xylene, ethylene dichloride, carbon tetrachloride, secondary amyl alcohol, or closely boiling naphthas are such solvents (94, 103, 147, 181, 316, 432). If a water-miscible solvent is used, the removal of the water from the vapors may be accomplished by drying agents, notably calcium carbide (103) or calcium chloride (316, 457).

Most polyhydric alcohol–fatty acid reactions are heterogeneous, at least during the initial stage. Consequently, the speed and course of reaction can be greatly influenced by efficient agitation. In many investigations no such agitation has been used. On the small scale, a rapid current of air, carbon dioxide, or another inert gas has often been considered sufficient agitation. The stirring and water-removing effect of a current of gas may be combined with the mixing action of mechanical stirring by introducing the gas into the center of the stirrer vortex, thus "whizzing" it throughout the reaction mixture. This procedure is stated to shorten the reaction time and to yield purer materials (73, 370).

Such currents of inert gases, e.g., carbon dioxide, nitrogen, or hydrogen, and also a vacuum, have been used to protect reaction mixtures, as well as to help the removal of moisture. Their influence has been studied on the reaction of glycerol with oleic acid (187). In this case, carbon dioxide gave products of good color, while nitrogen and reduced pressure did not. In no case was the rate of reaction influenced by the use of vacuum or inert gas under the conditions studied.

Information on reaction yield is not always given in the literature and is often ambiguous. In the patent literature, "yield" indicates, as a rule, the total of the useful product which need not be further purified and may contain a variety of ingredients. However, in technical papers "yield" refers to the purified products, generally excludes by-products and fractions which are not fully pure, and ignores solvents or auxiliary reagents. Products are often obtained from a reaction which has not been carried to completion. Sometimes the yield is based on one, not all, of the reactants used. It was, therefore, not possible to survey yield to advantage.

It was stated initially that polyhydric alcohol esters can be subdivided into two basic groups: completely esterified and partially esterified compounds. Esters of the former group are accessible by comparatively simple methods. Preparation of members of the latter group has given considerable trouble, because of the tendency to form mixtures. In direct esterification an excess of polyhydric alcohol is used to obtain incompletely esterified materials. A survey of the literature shows excesses of up to 33 moles of glycol for each mole of fatty acid (183, 259, 473, 474), and up to 11.5 moles of glycerol to 1 mole of fatty acid (28, 33, 38, 39, 42, 46, 59, 97, 103, 241, 249, 250, 253, 259, 260, 264, 314, 335, 352, 441, 457, 459, 537, 544, 548). With the higher polyhydric alcohols, such as erythritol, pentaerythritol, or mannitol, a greater excess seems to be of little value in securing a preponderance of lower esters (53, 56, 418, 477, 504, 518).

Continuous esterification at elevated temperatures is described in a series of patents. The polyhydric alcohol and the fatty acid are brought to react in vaporized form or in the form of mists, and are introduced through spray nozzles into a reaction chamber. The ester product collects in condensed form, owing to its higher boiling point (68, 93, 254, 270, 271, 272, 284, 285, 296, 300). This procedure may be carried out in special reactors designed to allow the mixture to pass through at varying speed or temperature (298).

When an excess of polyhydric alcohol is used, it will generally separate at the end of the reaction as an immiscible layer, or it may be washed out with water. In the case of products which are highly dispersible in water, such as polyglycerol esters, this is not possible, but washing may be carried out with certain concentrated salt solutions (185, 358, 359, 362, 363).

Excess fatty acids may be removed from polyhydric alcohol esters by neutralizing them to form soap, and extracting the esters with ether or with chlorinated solvents, such as dichloroethylene (90).

Ether alcohols, obtained by reacting alkylene oxides (or other anhydro derivatives of polyhydric alcohols) with the polyhydric alcohols, may be esterified with fatty acid in the manner described (274, 275, 288, 302, 308, 487, 488).

Partially esterified polyhydric alcohols may be further esterified with fatty acids, just as the polyhydric alcohols from which they are derived. This method does not furnish well-defined esters and offers no particular advantages as a reliable tool. Thus, glycerides were heated with an excess of fatty acid for 3 to 8 hr. at 200–270°C. (38, 39, 42, 253, 264), or with a sulfonic acid catalyst for 5 hr. at 120–130°C. (377). Mannitol diester has been further esterified in 20 to 30 hr. at 220–230°C. (53). Several technical applications are known: for instance, the neutralization of acidic oils (480, 536), the reësterification of certain partial esters of drying oil fatty acids (144), and the production of mixed esters (238, 241, 249, 250).

2. *Reaction of polyhydric alcohols with anhydrides of fatty acids*

Esterification with acid anhydrides is carried out in solvents at temperatures not exceeding 100°C. Materials such as glycerol, pentaerythritol, sorbitol, sugars, inositol, or quebrachitol may be reacted under the action of ketene gas, in the presence of condensation catalysts (sulfuric, hydrofluoric, perchloric acids; zinc chloride; benzenesulfonic acid) (145). Sucrose, dissolved in ten times its weight of monochloroacetic acid, may be reacted with fatty anhydrides, alone or mixed with acetic anhydride, using catalysts such as sulfuryl chloride or mag-

TABLE 6

Reaction of polyhydric alcohols with fatty acid halides

POLYHYDRIC ALCOHOL	TIME	REACTION TEMPERATURE	REMARKS	REFERENCES
	hours	°C.		
Ethylene glycol	24	In the cold; later 60	Pyridine	(514, 521, 555)
	48–72	In the cold	Quinoline	(564)
		Up to 180	No solvent used	(420)
1,2-Propylene glycol	2–3	95–100	No solvent used	(1)
			Pyridine	(514)
1,3-Propylene glycol			Pyridine	(515)
1,3-Butylene glycol			Pyridine	(514)
1,4-Butylene glycol			Pyridine	(514)
Glycerol	¾	125–130	Tertiary amine	(192, 269)
Erythritol			Formation of tri- and tetra-esters	(477)
Pentaerythritol	24	In the cold; later 60	Pyridine (6 moles)	(3)
			Pyridine	(274, 288, 487)
Mannitol	24	In the cold: later 60	Pyridine (10 moles)	(521)
Sorbitol	Several	Room	Pyridine	(274, 288, 487)
Dulcitol			Quinoline	(406)
l-Arabinose		50	Quinoline, chloroform	(406)
Glucose	24	Room; later 60	Pyridine (up to 15 moles	(60, 228, 231, 232, 521)
	8–12	60	Pyridine	(95)
		In the cold	Pyridine	(25, 265, 292, 465, 484)
	12	In the cold	Pyridine	(565)
Glucose (α)	4–6 (total 24)	Cold; −10, later 60	Pyridine (up to 25 moles)	(256, 565)
	72–96	15–18	Pyridine (up to 25 moles)	(256)
Glucose (β)	¼ – ¾ (total 24–72)	Cold; 10	Pyridine	(565)

TABLE 6—*Continued*

POLYHYDRIC ALCOHOL	TIME	REACTION TEMPERATURE	REMARKS	REFERENCES
	hours	°C.		
α-Methyl-*d*-glucoside.		50	Quinoline, chloroform	(405a, 406)
Sucrose.............	½ – 3 (total 4–48)	Room, 60	Pyridine (38 moles)	(256)
		70–80	Pyridine	(25, 265, 292, 465)
	½	125–130	Tertiary amine	(192, 269)
Raffinose............			Hendeca ester	(256, 406)
α-Monoglyceride.....	24	Cold	Pyridine, benzene	(377)

nesium perchlorate (371). Hydrol sugars and fatty anhydrides are reacted for 8 to 12 hr. at 100°C. (95, 120). α-Glucose pentacaproate has been obtained from glucose and caproic anhydride (256), and methylene glycol dimyristate from paraformaldehyde and myristic anhydride, by heating them to 100°C. with zinc chloride (514).

3. *Reaction of polyhydric alcohols with fatty acid halides*

Polyhydric alcohol esters may be obtained by dissolving an anhydrous polyhydric alcohol in a large excess of an anhydrous tertiary amine, such as pyridine, quinoline, or trimethylamine. A fatty acid halide, usually a chloride, is added to the solution, preferably dissolved in a chlorinated solvent such as chloroform. This method allows the use of low temperatures, but anhydrous working conditions are essential and the reagents are comparatively expensive (table 6). The reaction products are purified by pouring them into dilute aqueous mineral acid to remove all the excess amine and its halide salt. The ester product, recovered as a supernatant layer or by extraction, is treated to remove free acidity. This method is most suited to the preparation of the fully esterified product. Where pure partial esters are desired, certain modifications of the method are more suitable. These will be discussed later.

The amines may also be replaced by metallic halides which help to liberate hydrogen halide (192, 269). In another variation the polyhydric alcohol and the fatty halide are mixed directly, eliminating the free hydrogen chloride by means of a current of gas (1, 420). It has also been proposed to react the fatty acid halide with a tertiary amine first, filter off the precipitate of hydrochloride salt, and react the filtrate with a polyhydric alcohol (269, 283).

Evidence exists that a mixture of more and less esterified materials is formed with this method in at least some cases (256, 477, 484). No clearly defined yield data could be assembled.

4. Reësterification of fatty acid esters with polyhydric alcohols

One of the most widely used methods for the preparation of polyhydric alcohol esters is based upon the reësterification of fatty acid esters, and especially of the naturally available triglyceride fats. The reaction can proceed without a catalyst, but may be considerably speeded up if catalysts are used. Reësterification reactions involving polyhydric alcohols have been carried out along two different lines: (*1*) with elimination of the alcohol previously present in the fatty acid ester, usually by distillation (this is practical only if the polyhydric alcohol introduced for reaction has a higher boiling point than the alcohol present in the ester); (*2*) by allowing all ingredients to remain in the reaction product, even if esters of different alcohols are present in the resulting material.

TABLE 7

Reactions of polyhydric alcohols with alkyl esters

Polyhydric alcohol: glycerol

ESTER	TIME	REACTION TEMPERATURE	REMARKS	REFERENCES
	hours	°*C.*		
Ethyl......	102	100	Incomplete reaction; HCl catalyst	(38, 39)
		270	Incomplete reaction; autoclave, no stirring	(219)
	15	270–280	Open vessel, 94% conversion	(219)
Isoamyl....	15	270	Open flask, 100% conversion	(219)
Methyl.....		100	Incomplete reaction; HCl catalyst	(450)
	5, 48	70	Presence of acetone, HCl catalyst; forms isopropylideneglyceride	(450)
	24	100	Sodium methylate catalyst, in pyridine	(450)
Cetyl.......		200	Contradictory results; catalyst: zinc	(336, 404)
Alkyl.......			Sodium methylate or sulfonic acid catalysts; glycerol may be replaced by erythritol, arabitol, xylitol, mannitol, sorbitol, etc.	(204)

The most thoroughly studied example of the former type (reësterification with elimination of the lower boiling alcohol) is the reaction of alkyl esters with glycerol (219). It has been shown that under suitable conditions this reaction is reversible and is forced to go in the direction of glycerides only when the other alcohol is forced out by heat (table 7).

Only a few attempts have been recorded to replace the glycerol of triglycerides by higher boiling polyhydric alcohols, because of the high temperature required to distill off the glycerol. In the presence of a strong catalyst, sodium methylate, olive oil and tristearin have thus been reësterified with mannitol by raising the temperature to 275°C., while keeping the pressure at 14 mm. of mercury (190, 319, 354). Similarly, olive oil has been reacted with α-methyl-*d*-glucoside, by heating them to 220°C. under a pressure of 10 mm. of mercury (318). Sorbitol or pentaerythritol esters may be prepared similarly, using sodium methylate, but sulfuric or phosphoric acids have also been mentioned as catalysts (14, 143).

The second method, in which both the alcohol originally present and the alcohol added for reaction remain in the reaction product, has found very wide application in industry. Any type of alcohol can be used. Naturally, unless the polyhydric alcohol added is identical with the alkyl radical of the ester—usually glycerol—a mixture of esters will result. For many technical purposes, however, such mixtures have proven extremely useful. Often compounds with properties superior to those of the individual ingredients may be obtained. As in the case of direct esterification, the reaction runs only towards an equilibrium and the product is always a mixture (404, 405).

TABLE 8

Reësterification of triglycerides by polyhydric alcohols, without catalyst

POLYHYDRIC ALCOHOL	TIME	REACTION TEMPERATURE	REMARKS	REFERENCES
	hours	°C.		
Ethylene glycol...	1–2	200	Presence of ethanol, benzene, hydrogen gas under 90 atmospheres pressure has no effect; water slows reaction; autoclave	(338, 404, 405)
	9–13	200	Autoclave	(404)
Glycerol..........	1–9	200	Pyridine speeds reaction; ethanol has no effect	(404)
	2	200	Reflux	(57)
	22	200	Sealed tube	(38, 39)
	3	170–220	Partial reaction	(336)
	1–5	225–250	Partial or poor reaction; addition of monoglyceride speeds it	(336, 428, 429, 430, 435, 436, 470)
	1–5	270–290	Moisture formed in side reactions may be removed by partial reflux	(78, 79, 167, 329, 391, 392, 489, 490, 543, 564)
			No details available	(12, 28, 78, 79, 108, 109, 114, 115, 374, 529, 530)
Quebrachitol.....			No details available	(315)

Reësterification may be carried out without a catalyst but has been found to be speeded up greatly by catalysts, especially basic ones. Investigations on glycerol and pentaerythritol show this particularly well (57, 336). Of the few neutral and acid catalysts mentioned, it is stated that they are weak or ineffective (404). This type of reaction is reviewed in tables 8, 9, and 10.

As can be seen from these tables, the alkalis, alkali carbonates, alkali alcoholates, or generally any alkaline substance capable of forming soaps, as well as the soaps themselves, are the strongest and most frequently used reësterification catalysts.

TABLE 9

Reësterification of triglycerides by polyhydric alcohols, using alkaline catalysts

POLYHYDRIC ALCOHOL	TIME	REACTION TEMPERATURE	CATALYSTS AND CONDITIONS	REFERENCES
	hours	°C.		
Ethylene glycol....	1	200	Potassium carbonate	(404)
	2	150	Soap, alcoholate	(153, 427, 434)
Propylene glycol....	½–2	180–200	Potassium soap	(558)
Diethylene glycol...		Reflux	Sodium metal	(149)
Glycerol............	72	25	Sodium methylate, pyridine; poor reaction	(450)
	1–3	170–205	Potassium carbonate, sodium bicarbonate	(201, 202, 336)
	½ to 4	140–205	Sodium (potassium) glyceroxide or alcoholate; soap; alkali; sodium acetate	(54, 81, 82, 83, 84, 85, 149, 150, 151, 152, 158, 235, 239, 425, 426, 427, 434)
			Sodium metal	(426)
	2–5	200–220	Potassium carbonate; borax (poor); sodium hydroxide	(203, 336, 404)
	1½–5	240–290	Sodium (potassium) hydroxide; sodium carbonate; soap; sodium alcoholate	(249, 250, 303, 334, 336, 453, 471, 504, 506, 543)
	½	290	Trisodium phosphate, sodium carbonate; nitrogen gas	(564)
	1½	Reflux	Sodium hydroxide or glyceroxide; in dioxane	(458)
Polyglycerol........	1–3	250–265	Sodium hydroxide; sodium acetate	(160, 161, 168, 236, 238, 240, 241, 250, 451, 491, 492, 495)
Erythritol..........	5	220	Sodium hydroxide	(203)
Pentaerythritol.....	2½	205–210	Potassium hydroxide or alcoholate; alkalies	(14, 54, 57)
Sorbitol............		240–280	Alkali	(303)
Mannitol...........	5	220	Sodium hydroxide	(203)

The usefulness of certain basic salts, notably borax and trisodium phosphate, is doubtful. Other metallic oxides also act as catalysts, their effectiveness falling off in proportion to their alkalinity; calcium hydroxide or oxide, litharge, and magnesium oxide are preferred. The presence of water retards reësterification, and should be avoided (150, 151, 391, 392, 404, 499). Metals, particularly when combined with fatty acid, are fairly good catalysts (336).

While most of the reëesterifications are based on the triglycerides, the method has been shown to be capable of generalization, by reacting glycol with glycol dipalmitate in the presence of trisodium phosphate (564).

TABLE 10

Reësterification of triglycerides by polyhydric alcohols, using metal or metallic oxide catalysts

POLYHYDRIC ALCOHOLS	TIME	REACTION TEMPERATURE	CATALYSTS AND CONDITIONS	REFERENCES
	hours	°C.		
Ethylene glycol	1–2	170–190	Litharge	(558)
		180–200	Tin	(490, 494)
Glycerol	¼–½	200–280	Litharge	(54, 144, 170)
	1–2	200–280	Zinc oxide	(54, 404, 543)
	1–4	200–275	Calcium oxide, magnesium oxide, calcium glyceroxide	(54, 57, 301, 404, 543)
			Iron oxide, cobalt oxide	(54)
	3–5	170–250	Tin, zinc, aluminum metals, alone or with fatty acid	(224, 336, 480, 490, 494)
	1	230–250	Alumina, clay, infusorial earth; (hydrogen gas)	(10)
Erythritol		180–200	Tin	(490, 494)
Polyglycerol		180–200	Tin	(490, 494)
Pentaerythritol	3	220–270	Calcium oxide	(57)
	¼	280	Litharge, calcium oxide: effective. Magnesium oxide: less effective. Zinc, iron, cobalt oxides: ineffective	(54, 144)
Sorbitol, mannitol			Litharge	(144)
Mannitol, sorbitol		180–200	Tin	(490, 494)

Reësterification with alcohols is just one separate case of a more general type of reaction by which radicals in esters can be interchanged with alcohols, acids, or other esters. It may also be carried out simultaneously with esterification (336, 405).

Where the presence of soap in products resulting from reësterification is objectionable, methods have been suggested for its removal. The most usual method is its decomposition with acid (81, 82, 83, 84, 85, 235, 239, 453, 471). To avoid the formation of free fatty acid, the soap removal may be carried out by reaction with certain halogen-containing compounds, such as halohydrins, or with other compounds capable of yielding acid, such as the sulfuric esters of the polyhydric alcohols, thus yielding an ester and an inorganic salt (201, 202). The soap may also simply be removed by extraction of the ester with a suitable solvent (90, 331).

As in esterification, partial esters are formed if an excess of polyhydric alcohol is used, but unless sufficient soap is used or formed, the excess of polyhydric alcohol is not compatible with the resulting ester and must be drained or washed off. Under certain conditions, a very large excess of polyhydric alcohol can be kept homogeneously mixed with the product or reacted with the product (303, 458). Where the ester products are water soluble, unreacted excess of polyhydric alcohol may be removed by washing with certain salt solutions (185, 358, 359, 362, 363).

To produce special "cuts" of polyhydric alcohol esters by reësterification, the following procedure has been suggested: reësterification of triglycerides (with monohydric or polyhydric alcohols); fractionation of the products by liquid–liquid extraction, using mixtures of solvents which will separate into two liquid layers; and, finally reësterification of the fractionated esters (having higher or lower iodine values) with polyhydric alcohols, such as glycols, glycerol, erythritol, arabitol, xylitol, mannitol, or sorbitol. The preferred catalyst suggested is sodium methylate (203).

Reactions between polyhydric alcohols, fatty acids, and polyhydric alcohol esters must be considered reversible. Disproportionation of monoglycerides by heating them *in vacuo* at elevated temperatures is one interesting example. Monoglyceride thus turns into diglyceride and finally into triglyceride, with loss of free glycerol (220, 564).

5. *Etherification of polyhydric alcohol by reaction with partially esterified polyhydric alcohols*

As previously mentioned, reësterification of oils with polyhydric alcohols may be carried out with a large excess of polyhydric alcohol. This excess is said to react with the esterification product, yielding a homogeneous material (303, 458). Similarly, fatty acids may be reacted with a large excess of polyhydric alcohol, for example, in the presence of a mutual solvent, a water carrier, and a suitable catalyst, notably sulfuric or certain sulfonic acids (147, 432). Apparently the polyhydric alcohol present in excess reacts with the partial esters, forming esters of polyhydroxy ethers. Thus, mono- or di-glycerides either previously prepared, or formed *in situ*, form polyglycerol esters with excess glycerol. Water split out in reactions of this type has been observed to be more than that theoretically expected, a fact which has been explained as being caused by "side reactions" (57, 73, 151, 153, 264, 370). Etherification of glycols during reactions with fatty acids in the presence of dehydrating catalysts has also been mentioned (557).

B. PREPARATION FROM FULLY ESTERIFIED POLYHYDRIC ALCOHOLS

1. *Reaction of fully esterified polyhydric alcohols with water*

Polyhydric alcohol esters are formed by the reaction of polyhydric alcohols with fatty acids with the elimination of water. Reversing this reaction, it should be possible to obtain the partial esters which are formed during the hydrolysis of polyhydric alcohol esters. However, partial esters are very difficult to catch in this way, because most of them hydrolyze too quickly (378, 542a). A small quantity of mono- and di-glycerides can be isolated from glycerides that have been autoclaved with water for several hours (378). Similarly, losses of glycerol in fat splitting have been explained by the formation of partial glycerides (317). Naturally, this is not a practical method.

2. *Reaction of fully esterified polyhydric alcohols with concentrated sulfuric acid*

Hydrolysis of glycerides may be carried out with concentrated sulfuric acid in the cold. It was found (214, 218, 537) that if concentrated sulfuric acid was allowed to act on triglycerides at temperatures up to 70°C., 50 to 65 per cent of the material was hydrolyzed to free fatty acid and glycerol, while the remaining glycerides presented a mixture of triglycerides with diglycerides and a small percentage of monoglycerides. This seems to happen during the sulfonation of oils. Sulfonated oils contain considerable amounts of diglycerides in their neutral oil fraction (350).

3. *Reaction of fully esterified polyhydric alcohols with alkali*

Though in a survey in 1913 (378) it was stated that it had not been possible to find mono- or di-glycerides when interrupting the alkaline hydrolysis of triglycerides at an early stage, it was nevertheless admitted that their existence—at least temporarily—was possible. In later years, a number of patents were taken out along these lines, claiming that a mixture of mono-, di-, and tri-glycerides together with soap is obtained when triglycerides are treated with alkali. One such method involves heating the triglycerides to about 200–220°C., and adding alkali (anhydrous or as a concentrated aqueous solution), heating for 5 to 10 min., and cooling rapidly (249, 234, 235). The products may be plunged into cold water and their alkalinity partly neutralized with acids.

Another method is based upon the treatment of triglycerides with alkali in the cold in the presence of suitable solvents such as glycols or glycol-ethers (127, 330, 331, 505). While not yielding pure products, this method can obviously be used where the presence of soap is not undesirable.

4. *Reaction of fully esterified polyhydric alcohols with alcohols*

Polyhydric alcohol esters, such as triglycerides, can be reësterified with monohydric alcohols, forming monohydric alcohol esters. Initially, partial polyhydric alcohol esters are still found in the product, but finally polyhydric alcohol (glycerol, in the case of triglycerides) separates and the partial esters disappear. Materials of this type have been prepared and can be easily analyzed, after removal of the free alcohol, by distillation, or merely by determination of the acetyl value (1, 217, 219, 404, 469, 541).

C. PREPARATION FROM ANHYDRO DERIVATIVES OF POLYHYDRIC ALCOHOLS

A different approach to the preparation of polyhydric alcohol esters is by the addition reaction of anhydro derivatives of polyhydric alcohols and fatty acids. Such anhydro derivatives are the alkylene oxides (e.g., ethylene oxide, propylene oxide, glycide) or their halogen derivatives (e.g., epichlorohydrin). Instead of fatty acids, their anhydrides or halides may also be used.

To carry out this reaction, the low-boiling alkylene oxide is introduced into a pressure vessel containing the fatty acid and usually a catalyst. The reaction mixture is heated and stirred under pressure until enough of the alkylene oxide has been absorbed. A reaction of this type will normally yield only partial esters containing free hydroxyl groups (table 11).

Fatty acids may be esterified, and the products etherified by using an excess of the anhydro polyhydric alcohols, forming polyalkylene glycol esters, or polyalkoxy-polyhydric alcohol esters (table 12).

Partial polyhydric alcohol esters, obtained otherwise, may likewise be reacted with anhydro derivatives of polyhydric alcohols. An example is the reaction of a glycerol monoester with two or more parts of ethylene oxide (275, 302, 488).

Products obtained by reaction of anhydro-polyhydric alcohols with carboxylic acids may be purified by liquid–liquid extraction of the crude reaction products (279).

D. PREPARATION FROM SUBSTITUTED DERIVATIVES OF POLYHYDRIC ALCOHOLS

1. *Reaction of polyhydric alcohol halides with salts of fatty acids*

Reactions of halides of polyhydric alcohols with metallic salts of fatty acids (soaps) also yield polyhydric alcohol esters. Though this method has been used for numerous investigations in the past, its value has been reduced considerably by the discovery that, owing to acyl migration, fatty acid radicals are not necessarily introduced to take exactly the place of the halogen. The products are impure, and their purification is complicated.

The halide is mixed and heated with anhydrous soap for a number of hours, usually with stirring or shaking. The reaction has been carried out either in sealed tubes or under reflux. The polyhydric alcohol ester or esters and the unreacted fatty acid are recovered as an oil or solid, and there is a precipitate of inorganic halide salts. Unreacted organic halide and unreacted soap may also be present. The polyhydric alcohol ester may be purified by dissolving the oil layer in a suitable solvent (which will not dissolve soap and inorganic salts), such as ether, filtering, neutralizing the free fatty acid with alcoholic alkali, evaporating the solvent, and extracting and filtering once more. The extract thus obtained is washed with water, dried, and evaporated to yield the polyhydric alcohol ester. The yield from this type of reaction is stated to be poor.

TABLE 11

Condensation of fatty acids with anhydro derivatives of polyhydric alcohols

ANHYDRO POLYHYDRIC ALCOHOLS	TIME	REACTION TEMPERATURE	CATALYSTS, REMARKS	REFERENCES
	hours	°C.		
Ethylene oxide...	Several		Sodium hydroxide, autoclave	(496, 524)
	6	160	Zinc chloride, boric acid	(282)
		Elevated	Titanium dioxide, aluminum oxide, sodium chloride	(268)
Alkylene oxide....		Elevated	Mineral acid, acid salts, basic salts	(266, 366, 367, 368)
		Elevated	Fatty acid anhydride used	(516)
Glycidol..........	5	100	Secondary reaction, when iodohydrin is heated with silver soap; slow and incomplete	(221)
			Alkalies, alkaline salts, organic acids, or acid-reacting salts	(412a)

TABLE 12

Condensation of fatty acids with an excess of anhydro derivatives of polyhydric alcohols

ANHYDRO POLYHYDRIC ALCOHOLS	REACTION TEMPERATURE	CATALYSTS, REMARKS	REFERENCES
	°C.		
Alkylene oxide (ethylene, propylene)............	130–140	2 moles or more of oxide for 1 mole of fatty acid	(278)
Ethylene oxide..........	160	4 moles or more of oxide for 1 mole of fatty acid; sodium hydroxide, sodium alcoholate	(312)
Alkylene oxide..........	80–250	6 to 50 moles of oxide for 1 mole of fatty acid; acids, alkalies, active carbon or clay	(275, 302, 488)
Glycidol................	150	Sodium hydroxide: 2 moles or more for 1 mole of fatty acid	(276)
Epichlorohydrin........	50–100	Aluminum chloride, iron chloride, boron trifluoride, sodium aluminum chloride; chlorine atom may be reacted further	(291, 517)
Glycidol and other alkylene oxides...........		Alkalies, alkaline salts, organic acids, acidic salts	(412b)

TABLE 13

Reaction of polyhydric alcohol halides with fatty acid salts (soaps)

HALOHYDRIN	TIME	REACTION TEMPERATURE	METAL SALT USED; REMARKS	REFERENCES
	hours	°C.		
1-Chloroethanol	18–20	105–115	Ag	(474)
1,2-Bromoethane	Several	Reflux	Ag	(420, 563)
	10	180	Ag; sealed tube	(421a)
	3	130–140	K; open flask, nitrogen gas	(532)
		150	K; sealed tube	(532)
	48	140	Na	(88)
1,2-Chloroethane	10–15	180	K; excess halide yields chloroethyl esters	(351)
		200	Li	(518)
	1	150	Na; started as aqueous gel, dehydrated during reaction	(21, 22)
		160–180	K, Na, Li, Ca; in ethanol under pressure	(460)
1-Monoiodohydrin	2	100	K; forms diglycerol ester as by-product	(221)
		100	Ag; forms AgI, free acid, glycidol, impure esters	(221)
	4–10	110	Na; flask, reflux, or sealed tube	(13, 225, 252, 537)
		80–170	Na	(548)
	6	150–160	Na; reflux or sealed tube, CO_2	(441)
	4–6	140–150	Na (in dibutyl ether); sealed tube	(11, 344)
	12	160	K; hydrogen gas	(322)
	6	180	K; sealed tube, CO_2	(351)
	½	112	Pb; CO_2	(75)
1-Monochlorohydrin	10	180	Ag	(379)
2-Monochlorohydrin			K; halide used not pure	(171)
1,3-Dichlorohydrin	4	110	Na	(13)
	6–8	140–150	Na; sealed tube, CO_2	(225)
	8–9	140–150	Na	(172, 252, 537)
	10	170	Na; stoppered flask	(353)
	6–8	180	Na	(441)
			Na	(354, 459)
		120–140	K; CO_2	(216)
	9–10	140–150	K	(207, 208, 213)
	2½–9	160–170	K	(64, 213)
	12	160	K; hydrogen gas	(322)
	8½	160–170	K; in xylene	(539)
			K	(218)
	½	112	Pb; CO_2	(75)
	6	140–150	Pb	(537)

TABLE 13—(*Continued*)

HALOHYDRIN	TIME	REACTION TEMPERATURE	METAL SALT USED; REMARKS	REFERENCES
	hours	°C.		
1,2-Dibromohydrin	6–8	140–150	Na; sealed tube	(225, 449)
	72	120–135	Na; sealed tube	(449)
	6	175–180	Na; sealed tube	(441)
	12	180–200	Na; sealed tube	(449)
	6–8	150	K	(211)
	3½	160–170	K	(539)
	4	122	Pb; under pressure	(449)
1,2-Dichlorohydrin	10	112	Pb; CO_2	(75)
1,4-Dichloro-2,3-butanediol			Na; impure erythritol derivatives	(477)
2,3-Dichloro-1,4-dioxane	25	152–156	Free acid used, freeing HCl; in xylene	(510)
	14	161–190	Free acid used, freeing HCl; in xylene	(510)
Halohydrin			Any soap	(128, 488)

The preferred metallic salts for this reaction are sodium or potassium soaps, but lead and silver soaps have also been used. In the case of silver the reaction does not proceed satisfactorily. While silver chloride is formed at once, glycidol and free fatty acid form instead of the expected glycerol ester. On further heating, these materials yield a mixture of esters (221) (table 13).

This method has also been tried for further reaction of esters of polyhydric alcohol halohydrins, such as 1-lauro-3-chlorohydrin, with soaps of fatty acids (209).

2. Reaction of sulfuric acid esters of polyhydric alcohols with fatty acids

Sulfuric acid esters are formed in the reaction of polyhydric alcohols with cold concentrated sulfuric acid. With glycerol, diesters of sulfuric acid are formed, probably accompanied by small amounts of other esters. These sulfuric acid esters react with free fatty acids dissolved in concentrated sulfuric acid. At low temperatures, such as from 40° to 75°C., a homogeneous solution results, and after several hours fairly large quantities of polyhydric alcohol esters of fatty acid have formed. The original method of purifying these esters (by extracting the strongly cooled mixture with ice-cold ether and diluting this with ice-cold water) gives poor yields, because of hydrolysis and side reactions (such as the formation of ethyl esters of fatty acids). This is avoided by pouring the reaction mixture into ammonium sulfate solution, followed by washing and then extracting with ether (59, 60). High-molecular-weight fatty acids (e.g., stearic) give better ester yields with this method than do fatty acids of lower molecular weight (e.g., lauric).

A considerable amount of unreacted fatty acid is recovered in the crude ether extract. This must be neutralized into soap and removed as such. (See table 14.)

TABLE 14

Reaction of sulfuric acid esters of polyhydric alcohols with fatty acids

POLYHYDRIC ALCOHOL	TIME	REACTION TEMPERATURE	REMARKS	REFERENCES
	hours	°C.		
Glycerol	3	70	Glycerol:H_2SO_4, 1:4 by weight; fatty acid: H_2SO_4, 2:3 by weight; yield varies from 34 to 80% according to method of purification	(206, 207, 537, 548)
	4	50–60	Glycerol:H_2SO_4, 1:4.35 by weight; yield varies	(213, 215, 538)
Mannitol	3	65–75	1 g. mannitol to 7.5–10 cc. of H_2SO_4; yields mannide, mannitan esters; yield, 50%	(58, 59)
		38–40	Mannitol:H_2SO_4, 1:20 by weight; yield varies from 45 to 85% according to method of purification; mannitan, isomannide ester	(59, 60, 323)

3. Interchange of polyhydric alcohol esters of volatile acids with fatty acid esters of volatile alcohols

Another method of making polyhydric alcohol esters is by the reaction of short-chain fatty acid esters of polyhydric alcohols, such as glycol diacetate, with short-chain monohydric alcohol esters of long-chain fatty acids, such as methyl stearate. The two volatile radicals combine to form a volatile ester, methyl acetate, leaving the polyhydric alcohol ester behind. This reaction may be carried out at relatively low temperature (414).

E. PREPARATION FROM "PROTECTED" DERIVATIVES OF POLYHYDRIC ALCOHOLS

1. Reaction of polyhydric alcohol halohydrins with fatty acid halides

The first step of this reaction consists in treating a polyhydric alcohol halohydrin (e.g., monochloroethanol, 1-monoiodopropanediol, 1,3-dichloropropanol) with a fatty acid halide at room temperature or at a slightly elevated temperature. The hydrogen halide liberated may be driven off by a current of air (210), or may be neutralized by a tertiary amine such as quinoline (8, 20, 177). An attempt to use this for a reaction with erythritol 1,4-dichlorohydrin has also been recorded (477).

The halogen-containing ester is now treated at 120–130°C. with an equal weight of silver nitrite to remove the halogen groups (171, 172, 208, 209, 210, 212, 218, 322, 459, 539). This procedure requires 5–14 hr. and is usually carried out in an atmosphere of hydrogen. Silver oxide has also been used (420). A much better yield may be obtained if the reaction is carried out in a solvent, such as 90 per cent ethyl alcohol. Seventy-five per cent of the expected yield has been obtained thus after only half an hour (8, 20, 177).

As a result of acyl migration, however, the partial esters produced do not necessarily contain the acyl group where the hydroxyl group had been in the halohydrin; hence this method has little value as a reliable tool. 2-Acylglycerides prepared by it were found to be merely 1-acylglycerides, which may readily be obtained otherwise (171, 172).

Esters obtained by this method are purified by ether extraction (in the presence of a little hydrochloric acid to remove all excess silver salt), neutralization, and filtration.

2. Reaction of isopropylidene derivatives of polyhydric alcohols with fatty acid halides, and tertiary amines

The first successful method to direct the fatty acid radical into a well-defined position in the glycerol molecule was found in the acylation of isopropylidene derivatives of glycerol. In reacting glycerol with acetone by the action of dry hydrogen chloride gas, 1,2-isopropylideneglycerol is always formed. After reacting this with the fatty acid halide, usually in the presence of pyridine or quinoline, the isopropylidene group is removed by short contact in the cold with concentrated hydrochloric acid, dilution with cold water, and purification of the water-insoluble ester.

While thus far recorded only in connection with glycerol esters, this method is likely to be of general value, as the formation of isopropylidene derivatives of other polyhydric alcohols, such as mannitol, has been shown to be possible, and it is likely that they will lend themselves to the same reaction.

With glycerol, this method is the most reliable known to obtain 1(or alpha)-monoesters. It has been used to prove that all older methods yield primarily 1-acyl or 1,3-acyl esters with glycerol. The method usually gives good yields.

The isopropylidene group is introduced by allowing anhydrous, freshly distilled glycerol to stand with acetone saturated with dry hydrogen chloride over fused anhydrous sodium sulfate. The hydrogen chloride in excess is then removed, the acetone distilled off, and the isopropylidene glycerol itself is rectified by distillation.

The isopropylidene product is reacted with a fatty acid halide (chloride) and a tertiary amine in the usual manner, usually at room temperature or below. Purification of the isopropylideneglycerol ester consists in removal of the pyridine or quinoline by pouring it into *N*/2 sulfuric acid in the presence of ether, washing, and recovery of the ester. A variation of the method, much simplified, has also been proposed (376): isopropylideneglycerol is reacted with the fatty acid itself by passing in dry hydrogen chloride gas for 15 min., and the product is poured into water.

The isopropylidene group is then removed from the ester by the action of concentrated hydrochloric acid, at room temperature, for about 30 min. (8, 8a, 20, 23, 52, 64a, 65, 66, 171, 176, 376, 450, 533, 548). This may be carried out in the presence of a solvent, such as ether. For esters of the lower members of the fatty acid series, such as lauric acid, the hydrolysis must be carried out at −15°C. to 0°C. and must not last more than 5 to 10 min. (171, 176, 450, 459, 564). Another method of hydrolysis consists in treatment with $N/4$ sulfuric acid at 45°C., followed by neutralization with barium hydroxide (20).

When glycerol and the methyl ester of a fatty acid are refluxed in acetone in the presence of hydrogen chloride gas, a large quantity of isopropylidene monoglyceride forms, from which monoglyceride can be recovered (450).

3. Reaction of benzylidene derivatives of polyhydric alcohols with fatty acid halides and tertiary amines

A second method developed to yield well-defined glycerol derivatives is based upon the reaction of benzaldehyde with glycerol, which yields 1,3-benzylideneglycerol. The purified benzylideneglycerol is treated at room temperature for 18–24 hr. with fatty acid chloride in the presence of a tertiary amine, such as pyridine, and is purified as described previously for this type of reaction.

The purified 2-acylbenzylideneglycerol is suspended in absolute alcohol, and hydrogenated in the presence of a palladium black catalyst for 1½ to 2 hr. at room temperature. A 2(or beta)-monoglyceride can be obtained by crystallization from the resulting solution (36, 121a, 522).

This method was the first one which yielded true 2-monoglycerides, and may yet find more general application; benzylidene derivatives of higher polyhydric alcohols, such as mannitol or sorbitol, have already been prepared.

4. Reaction of carbobenzyloxy derivatives of polyhydric alcohols with fatty acid halides and tertiary amines

A recent method for the formation of 1,2-acylated glycerol (122) is the following: 3-monosodium glyceroxide is prepared and reacted with benzylchloroformate ($C_6H_5CH_2OCOCl$) in dry benzene, yielding 3-carbobenzyloxyglycerol. This glycerol compound is reacted with a fatty acid chloride in the presence of quinoline, yielding a 1,2-diacylated material. The resulting 3-carbobenzyloxy-1,2-diglyceride is purified, suspended in absolute alcohol, and treated with hydrogen in the presence of palladium black. The 1,2-diglyceride can be recovered from the solution.

5. Reaction of trityl ethers of polyhydric alcohols with fatty acid halides and tertiary amines

Glycerol forms well-defined 1-mono- and 1,3-ditrityl (or triphenylmethyl) ethers. These may be used for the preparation of 2-monoglycerides and 1,2-diglycerides. Initially, the removal of the trityl group with hydrogen bromide or hydrogen chloride gas, yielding triphenylmethyl halide, was attempted (324, 549, 550, 551), but was found to cause acyl migration. By carrying out the removal of the trityl group by hydrogenation in the presence of palladium-charcoal or platinum dioxide catalyst, triphenylmethane and 2-monoglyceride or 1,2-diglyceride form without acyl migration (123, 552, 554).

This method may well lend itself to the preparation of other polyhydric alcohol esters (553). For instance, 1,6-ditrityl mannitol has already been prepared.

6. Reaction of the benzyl ethers of polyhydric alcohols with fatty acid halides and tertiary amines

Another method for the preparation of 1,2-diglycerides (179, 512) consists in introducing a benzyl ether group into isopropylideneglycerol, removing the isopropylidene group by refluxing with dilute sulfuric acid, and reacting the resulting 1-benzyl ether of glycerol with fatty acid chloride in the presence of a tertiary amine in the known manner. The 1,2-diglyceride is then obtained by catalytic hydrogenation of the purified product. The use of acetic acid as a solvent for the hydrogenation may well have caused the discrepancy in melting points of the products obtained by this method and by the trityl method.

7. Reaction of sulfuric acid esters of halohydrins of polyhydric alcohols with fatty acids

A variation of a method previously reported consists in preparing sulfuric acid esters from halohydrins such as glycerol monochlorohydrin or dichlorohydrin by the action of concentrated sulfuric acid (208, 214) or of chlorosulfonic acid (537) in the cold, and by reacting the product with fatty acid. In the former method, the fatty acid is introduced dissolved in two times its weight of concentrated sulfuric acid. Reaction is carried out for from 1 to 3 hr. at 45–70°C., and the ester product is purified by diluting with ether, washing, neutralizing the usually large excess of unreacted fatty acid, and extracting (sometimes distilling). The halogen is removed by heating with silver nitrite at 110–120°C. This requires at least equal weights of silver nitrite, gives a poor yield, and causes acyl migration, thus offering no advantages over other methods.

F. PREPARATION FROM RELATED COMPOUNDS BY SPECIAL METHODS

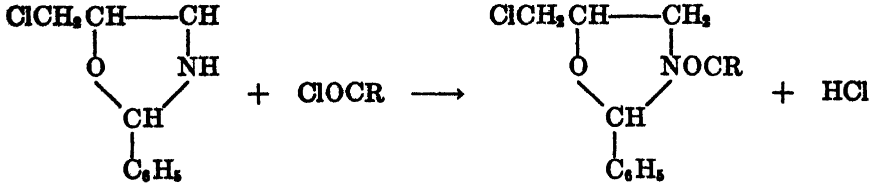
Special methods which have been tried for the preparation of certain polyhydric alcohol esters are briefly reviewed here because they may offer more general application in the future.

The oxidation of allyl esters of fatty acids with potassium permanganate in acetone leads to 1-monoglycerides, but in very poor yields (30 per cent maximum) (450).

The catalytic reduction of diacyldihydroxyacetone yields mixtures of 1,2- and 1,3-diglycerides. No details of this method were found (222).

The addition of hypoiodous acid to an allyl ester of fatty acid leads to 1-acyl-2-iodohydrin; this, on reaction with an alkali soap, is said to form a 1,2-diglyceride, but most likely the product is a 1,3-diglyceride, owing to acyl migration (191).

1-Monoglycerides have been prepared as follows (35): Phenylchloromethyloxazolidine is reacted with a fatty acid chloride and pyridine, yielding 2-phenyl-3-acyl-5-chloromethyloxazolidine:



(R = alkyl)

This is split by fuming hydrochloric acid, removing benzaldehyde. The product, $ClCH_2CHOHCH_2NHOCR$ (3-chloro-2-hydroxy-1-acylaminopropane), can be caused to rearrange to the hydrochloride of 3-acylated-2,3-dihydroxypropylamine by boiling it with water. The product, $RCOOCH_2CHOHCH_2NH_2 \cdot HCl$, will form 1-monoglyceride on diazotization with nitrous acid.

Glycol diesters have been prepared by reaction of the cyclic glycol-ether dioxane by reaction with fatty acid halides, thus opening the ether linkages (547).

II. PROPERTIES OF POLYHYDRIC ALCOHOL ESTERS

Considerable experimental data have been assembled regarding the physical and chemical properties of the polyhydric alcohol esters. Yet only certain esters have been investigated thoroughly and much of the data are not reliable because the esters were made by faulty methods. A good deal is known about the properties of the fatty acid esters of ethylene glycol, propylene glycol, glycerol, mannitol, and glucose, but very little or nothing at all was found about the others, notwithstanding the fact that many of these other compounds are frequently mentioned in the patent literature.

Most of the common data have been compiled in tables 16 to 23. Chiefly, these include the melting points, density, refractive index, solubilities, boiling ranges, optical rotation, and some chemical data such as saponification, iodine, and acetyl values. Certain other, less usual facts are available which do not stand out in the tables. They are briefly discussed here.

A. TRENDS

Certain regularities and trends are revealed by a study of the physical and chemical properties of the polyhydric alcohol esters. Unfortunately, the available information is too incomplete to enable one to arrive at more definite conclusions with authority.

It is well known, of course, that the melting points and boiling points of the polyhydric alcohol esters increase in proportion to the increase of the chain length of their acid radicals, while, in general, their solubility decreases. It is also known that lower melting and more soluble esters are formed from the unsaturated carboxylic acids than from the corresponding saturated acids.

Among the esters of the glycols, the diesters appear to be distinctly higher melting than the monoesters (262, 263). On the other hand, the monoesters of glycerol are higher melting than the corresponding diesters (259). The melting points of the esters of erythritol, mannitan, and glucose, too, seem to increase in proportion to an increasing number of unesterified alcoholic hydroxyl groups. The 2- and the 1,2-glycerides are distinctly lower melting than the 1- and 1,3-glycerides.

The esters of polyhydroxy ethers, such as diethylene glycol, triethylene glycol, polyglycols, polyglycerols, and hydroxyalkyl ethers of polyhydric alcohols, appear, from the meager data available, to be soluble in a wider range of solvents and to have lower melting points than the esters of the corresponding polyhydric alcohols. Among the derivatives of mannitol (and probably of the other hexitols), the melting point of certain partly acylated materials (e.g., diesters) drops, while the solubility rises, as hydroxyl groups are eliminated with the formation of inner ethers, such as mannitan or mannide.

TABLE 15

Melting points of palmitates in °C.

	MONO	DI	TRI	TETRA	PENTA	HEXA	OCTA	HENDECA
Methylene glycol		49.5						
Ethylene glycol	52.5	72						
1,2-Propylene glycol	55–56	69.5–70						
1,3-Propylene glycol	42–43.5	56.5						
1,3-Butylene glycol		39–40						
1,4-Butylene glycol		63						
Glycerol: 1-; 1,3-	77	72.5	65					
Glycerol: 2-; 1,2-	69	64						
Erythritol		99.5–101	81–8					
l-Arabinose				69.5				
α-Methyl-*d*-glucoside			77	69				
α-Glucose					72–75			
β-Glucose					68–72			
Mannitol						64.5		
Dulcitol						74		
Sucrose							54–55	
Raffinose								52–3

To indicate roughly the melting-point relations of the various polyhydric alcohol esters, the palmitates (which are the most thoroughly documented) may be chosen for comparison (table 15).

B. MELTING POINTS

The melting points given in the literature show large discrepancies (20, 450). In many cases it is necessary to blame this on lack of purity of the material investigated, such as may be caused by impure raw materials or by untrustworthy methods of preparation. However, it has been shown reliably that certain polyhydric alcohol esters, notably the glycerides, exist in several poly-

TABLE 16

*Physical and chemical properties of glycol esters**

ESTER	MELTING POINT °C.	SOLUBILITY	OTHER DATA	REFERENCES
Methylene glycol dimyristate	49.5	Acetone: moderately soluble, crystallizes on cooling Benzene, carbon tetrachloride: soluble		(514)
Ethylene glycol				
Monolaurate	27.5	Ether: very soluble hot, cold		(259)
Dilaurate	49; 52; 54	Acetone: moderately soluble, crystallizes on cooling Ether: soluble hot, crystallizes on cooling Benzene, carbon tetrachloride: easily soluble	Boils at 188°C. (0 mm. Hg)	(45, 259, 351, 398a, 514, 515)
Dimyristate	63; 64	Acetone: moderately soluble, crystallizes on cooling Ether, benzene, carbon tetrachloride: soluble	Boils at 208°C. (0 mm. Hg)	(351, 514, 515)
Monopalmitate	47.5; 48; 49; 51–52.5; 51.5	Ethanol (absolute), in grams per 100 g.: 1.62 (0°C.); 5.76 (7.4°C.); 10.67 (16°C.); 24.08 (25°C.) Acetone, ether: soluble, crystallizes on cooling Chloroform: crystallizes on cooling	Density (at melting point), 0.8786 Refractive index, 1.4411 Molecular weight: 297 (in camphor), 270 (in retene); calculated, 300	(183, 249, 408, 473, 474, 564)

Dipalmitate	65; 68.7–68.9; 69; 70; 70.5; 72	Ethanol (absolute), in grams per 100 g.: 0.018 (0°C.); 0.087 (25°C.); 0.109 (28°C.); 0.31 (38°C.) Acetone: moderately soluble Ethyl acetate: soluble Ether: crystallizes on cooling Benzene, chloroform, carbon tetrachloride: easily soluble	Boils at 226°C. (0 mm. Hg) Density (at melting point), 0.8594 Refractive index, 1.4378 Crystals: birefringent radial-symmetrical masses	(2, 45, 259, 351, 398a, 408, 421a, 473, 474, 514, 515, 521, 555, 564)
Monomargarate (heptadecoate)	50.2; 53.2	Ethanol (absolute), in grams per 100 g.: 1.72 (0°C.) Ethanol (hydrous): very soluble, crystallizes on cooling	Refractive index, 1.4440	(473, 474)
Dimargarate (heptadecoate)	65.5; 70.4	Ethanol (absolute), in grams per 100 g.: 0.024 (0°C.); 0.101 (25°C.) Ethanol (hydrous): poorly soluble, crystallizes on cooling	Density (at melting point), 0.8605 Refractive index, 1.4392	(473, 474)
Monostearate	56; 58.5	Ethanol (absolute), in grams per 100 g.: 0.67 (0°C.); 4.17 (25°C.); 10.61 (29°C.) Ethanol (hydrous): soluble Ether: very soluble cold	Density (at melting point), 0.8780 Refractive index, 1.4310	(259, 473, 474)
Distearate	73; 75–76.5; 75.8; 76; 77; 79	Ethanol (absolute), in grams per 100 g.: 0.01 (0°C.); 0.028 (25°C.); 0.037 (28°C.); 0.112 (40°C.) Ether: soluble hot, crystallizes on cooling	Boils at 241°C. (0 mm. Hg) Density (at melting point), 0.8581 Refractive index, 1.4385	(45, 103, 103a, 259, 351, 398a, 420, 421a, 473, 474, 555, 563)

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* Certain data have already been given in the text, but all references to cover them are entered here, because many original papers were not accessible to the author for detailed information.

TABLE 16—*Continued*

ESTER	MELTING POINT	SOLUBILITY	OTHER DATA	REFERENCES
	°C.			
Ethylene glycol—*Cont.* Distearate—*Cont.*		Benzene, nitromethane: soluble	Molecular weight: 497, 524, 530, 532 (in benzene); 489, 496, 575, 580 (in nitromethane); calculated, 594.6 Crystals: birefringent radial-symmetrical masses Saponification value: 187.5, 189.4; calculated, 188.7	
Monoöleate	1		Boils at 190–200°C. (0.05 mm. Hg); 200–220°C. (7.3 mm. Hg) Refractive index, 1.4600 (27°C.) Saponification value, 165.9; calculated, 170 Acetyl value, 153.5	(88, 259, 404)
Dioleate		Ether: soluble	Boils at 183–185°C. (3 mm. Hg) Density, 0.906 (25°C.) Refractive index, 1.4492 (70°C.) Specific refraction, 0.3038; calculated, 0.305	14, 421a, 424, 518, 532)

			Saponification value: 190.5, 192; calculated, 190 Iodine value: 84.5, 79.8–81	
Dilinoleate			Density, 0.916 (25°C.) Specific refraction, 0.30648; calculated, 0.302 Saponification value, 189.5; calculated, 191 Iodine value, 169.6	(414, 424)
Dieleostearate			Density, 0.921 (35°C.) Molecular weight, 556 (in stearic acid); calculated, 586 Crystallizes on standing (forms oxidation products) Saponification value, 211.5; calculated, 191 Maleic anhydride addition value, 79.8	(386, 414)
Monoester of coconut oil fatty acid	28–30; 42	Ethanol, acetone: soluble Isopropanol, glycol, glycerol, toluene, naphtha, linseed oil, mineral oil: soluble		(158, 200)

TABLE 16—*Continued*

ESTER	MELTING POINT	SOLUBILITY	OTHER DATA	REFERENCES
	°C.			
Ethylene glycol—*Cont.*				
Monoester of commercial stearic acid	59–61	Ethanol, acetone: soluble hot, crystallizes on cooling Toluene: soluble hot, cold Naphtha, mineral oil: soluble hot		(200)
Monoester of commercial oleic acid		Ethanol, acetone, toluene, naphtha, mineral oil: soluble	Crystallizes on standing	(200)
Monoester of rapeseed oil fatty acid			Saponification value, 167 Viscosity, 6.74° Engler (20°C.); 10.74° Engler (10°C.)	(258, 566)
Monoester of linseed oil fatty acid			Density, 0.9214 (30°C.) Refractive index, 1.4748 (20°C.) Saponification value, 171; calculated, 174 Acetyl value, 168	(73)
Diester of linseed oil fatty acid			Boils at 212°C. (2.5 mm. Hg); 250°C. (30 mm. Hg)	(139, 370)

			Refractive index, 1.4856, 1.4779 Molecular weight, 603; calculated, 602 Saponification value: 203.7, 294.2; calculated, 187 Iodine value: 160.2, 125.7	
Monoester of tung oil fatty acid...........			Density, 0.9495 (30°C.) Refractive index, 1.4956 (20°C.) Saponification value, 175; calculated, 176 Acetyl value, 130	(73)
Monoester of castor oil fatty acid........		Ethanol, acetone: soluble Toluene, naphtha: poorly soluble Mineral oil: insoluble		(200)
1,2-Propylene glycol Dilaurate........... ..	35	Acetone: crystallizes on cooling Benzene, carbon tetrachloride: easily soluble		(514, 515)
Dimyristate..........	41.5	Acetone: crystallizes on cooling Benzene, carbon tetrachloride: easily soluble		(514, 515)
Monopalmitate........	54.3; 55–56	Ethanol, in grams per 100 g.: 0.0193 (0°C.); 0.0907 (15°C.)	Refractive index, 1.4405	(261, 262)

TABLE 16—Co

ESTER	MELTING POINT	SOLUBILITY	OTHER DATA	REFERENCES
	°C.			
1, 2-Propylene glycol—*Cont.*				
Dipalmitate	52.5–54.5; 68.8; 69.5–70	Ethanol, in grams per 100 g.: 0.00516 (0°C.); 0.0115 (15°C.) Acetone: moderately soluble, crystallizes on cooling Benzene, carbon tetrachloride: easily soluble	Refractive index, 1.4364	(262, 408, 514, 515)
Monostearate	59.5	Ethanol, in grams per 100 g.: 0.0211 (0°C.); 0.034 (15°C.)	Refractive index, 1.4424	(262)
Distearate	40; 72.3	Ethanol, in grams per 100 g.: 0.0012 (0°C.); 0.0063 (15°C.) Ether: soluble	Refractive index, 1.4366 Saponification value, 190.8; calculated, 184.7	(1, 262)
Dioleate			Saponification value, 191.5; calculated, 186	(1)
Monoester of coconut oil fatty acid		Ethanol, acetone, toluene, naphtha, mineral oil: soluble		(200)
Ester of commercial stearic acid	33–35; 37; 37–39	Ethanol: soluble hot Acetone: soluble hot, cold Toluene, naphtha, mineral oil: soluble hot		(49, 50, 200)
Monoester of commercial oleic acid		Ethanol, acetone, toluene, naphtha, mineral oil: soluble		(200)

Ester of linseed oil fatty acid			Boils at 218–220°C. (5 mm. Hg) Refractive index, 1.4812 Saponification value, 204.58; calculated, 182 Iodine value, 131.1 Molecular weight, 403; calculated, 616	(139)
Monoester of castor oil fatty acid		Ethanol, acetone, toluene, naphtha: soluble Mineral oil: poorly soluble, soluble hot		(200)
1,3-Propylene glycol				
Dilaurate	38–39	Acetone: crystallizes on cooling		(515)
Dimyristate	49–49.5	Acetone: crystallizes on cooling		(515)
Monopalmitate	42–43.5			(409)
Dipalmitate	54.2–55.5; 55.5; 56.2; 56.5	Ethanol, in grams per 100 g.: 0.0244 (0°C.); 0.0517 (15°C.) Acetone: crystallizes on cooling	Refractive index, 1.4374	(262, 408, 409, 515)
Monostearate	60.5	Ethanol, in grams per 100 g.: 0.01431 (0°C.); 0.0305 (15°C.)	Refractive index, 1.4437	(262)
Distearate	64.7	Ethanol, in grams per 100 g.: 0.00126 (0°C.); 0.00381 (15°C.)	Refractive index, 1.4397	(262)

TABLE 16—*Concluded*

ESTER	MELTING POINT	SOLUBILITY	OTHER DATA	REFERENCES
	°C.			
1,3-Butylene glycol				
Dilaurate	16.5	Acetone–petroleum ether: soluble, crystallizes on cooling Benzene, carbon tetrachloride: soluble		(514, 515)
Dimyristate	29.5–31	Acetone: soluble Benzene, carbon tetrachloride: soluble Acetone–petroleum ether: crystallizes on cooling		(514, 515)
Dipalmitate	39–40	Acetone: soluble Benzene, carbon tetrachloride: soluble Acetone–petroleum ether: crystallizes on cooling		(514, 515)
1,4-Butylene glycol				
Dilaurate	45.5	Acetone: poorly soluble Benzene, carbon tetrachloride: soluble		(514)
Dimyristate	55	Acetone: poorly soluble Benzene, carbon tetrachloride: soluble		(514)
Dipalmitate	63	Acetone: poorly soluble Benzene, carbon tetrachloride: soluble		(514)

morphous forms, and thus have more than one melting point (376, 377, 450). The glycerides occur in an unstable (alpha), a stable (beta), and some also in a metastable (beta′) form. The conversion from the unstable to the stable form at the melting temperature of the lower melting form is almost instantaneous for monolaurin, but requires more than 45 min. for monostearin (376, 377, 450). The stable (beta) form is the one usually obtained by crystallization from solvents; the unstable (alpha) form, which is lower melting, usually forms first when a fused glyceride is cooled. Melting points of glycerides may change on storage (207, 210), and sometimes differ with the methods and solvents used for crystallization (221).

A study of the cooling curves of glycerides reveals further conversion points ("breaks"). Other properties, such as the dielectric constant and the x-ray pattern, also change at these points.

C. DIELECTRIC CONSTANT

The dielectric constants of 1-monostearin and monomyristin have been determined at frequencies of 1000 and 4400 kilocycles per second (47, 48). Sharp changes of the dielectric constant take place at conversion points of the various forms into one another. These forms, their dielectric constants, and their conversion points are given below:

ESTER	DIELECTRIC CONSTANT	CONVERSION (MELTING) POINT
		°C.
1-Monostearin:		
Unstable form	4.96 (at 40°C.)	74
Metastable form		79
Stable form	2.40 (at 40°C)	81.5
1-Monomyristin:		
Unstable form	8.58 (at 38.2°C)	56
Metastable form	2.86 (at 40°C.)	67.5
Stable form	2.41 (at 40°C.)	70.5

These determinations were carried out at 1000 kilocycles per second.

D. CONVERSION OF 2(OR β)- TO 1(OR α)-GLYCERIDES

After satisfactory methods for the preparation of 2-monoglycerides and 1,2-diglycerides had at last been developed, work was done to determine their stability. They were found to be readily converted by acids and alkalies, which cause acyl migration, explaining the large amount of wasted effort to obtain these glycerides. It has now been shown that hydrochloric acid as dilute as 0.0067 *N* caused marked conversion to the alpha ester within 24 hr., although 0.005 *N* hydrochloric acid did not. A 0.0125 *N* ammonium hydroxide solution caused conversion, but a 0.01 *N* solution did not (121a, 122).

TABLE 17

*Physical and chemical properties of ether-glycol esters**

ESTER	MELTING POINT	SOLUBILITY	OTHER DATA	REFERENCES
	°C.			
Diethylene glycol Dilaurate	31	Glycol, glycerol, butyl acetate, linseed oil: soluble	Boils at 200°C. (11 mm. Hg) Density, 0.929 (24°C.) Molecular weight, 522; calculated, 470.5	(94, 158)
Monoester of coconut oil fatty acid	17–18	Ethanol, acetone: soluble Toluene, naphtha, mineral oil: moderately soluble		(200)
Diester of coconut oil fatty acid		Ethanol, isopropanol: soluble Toluene, naphtha: soluble		(94, 158)
Monoester of commercial myristic acid	35	Ethanol: soluble hot Acetone: soluble hot, cold Toluene, naphtha, mineral oil: moderately soluble		(200)
Monoester of commercial stearic acid	42–43; 55; 58	Ethanol, acetone, toluene, naphtha, mineral oil: soluble hot, crystallizes on cooling		(29, 200, 257, 567)
Monoester of commercial oleic acid		Ethanol, acetone, esters, toluene, naphtha, mineral oil: soluble		(29, 200, 567)
Diester of linseed oil fatty acid			Refractive index, 1.4777	(370)

Monoester of castor oil fatty acid.....		Ethanol, acetone, toluene, naphtha: soluble Mineral oil: poorly soluble		(200)
Triethylene glycol				
Ester of cocoanut oil fatty acid.........		Ethanol, glycol, naphtha, linseed oil: soluble		(158)
Diester of commercial stearic acid		Toluene, benzene, turpentine: soluble		(32)
Tetraethylene glycol				
Monoester of commercial stearic acid..	29–30	Ethanol, acetone, toluene, naphtha, mineral oil: soluble hot	Disperses in hot water	(200)
Diester of commercial stearic acid.....	32–33	Ethanol: soluble hot Acetone: poorly soluble Toluene: soluble hot, cold Naphtha: poorly soluble Mineral oil: soluble	Disperses in hot water	(200)
Hexaethylene glycol				
Monoester of commercial oleic acid....		Ethanol, acetone, toluene: soluble Naphtha, mineral oil: moderately soluble	Disperses in water	(200)
Nonaethylene glycol				
Monoester of coconut oil fatty acid ...		Ethanol, acetone, toluene: soluble Naphtha: moderately soluble Mineral oil: insoluble or poorly soluble	Dissolves colloidally in water	(200)
Diester of coconut oil fatty acid......		Ethanol, acetone, toluene, naphtha: soluble Mineral oil: soluble hot	Disperses in water	(200)

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* Certain data have already been given in the text, but all references to cover them are entered here, because many original papers were not accessible to the author for detailed information.

TABLE 17—*Co*

ESTER	MELTING POINT	SOLUBILITY	OTHER DATA	REFERENCES
	°C.			
Nonaethylene glycol—*Cont.*				
Monoester of commercial stearic acid..	27–29	Ethanol, acetone, toluene: soluble Naphtha, mineral oil: soluble hot or poorly soluble	Disperses or dissolves colloidally in water	(200)
Diester of commercial stearic acid.....	29–31	Ethanol, acetone, toluene: soluble Naphtha, mineral oil: soluble hot	Disperses in hot water	(200)
Monoester of commercial oleic acid ...		Ethanol, acetone, toluene: soluble Naphtha: moderately soluble Mineral oil: insoluble or poorly soluble	Disperses or dissolves colloidally in water	(200)
Diester of commercial oleic acid.......		Ethanol, acetone, toluene, naphtha, mineral oil: soluble	Disperses in water	(200)
Monoester of castor oil fatty acid.....		Ethanol, acetone, toluene: soluble Naphtha, mineral oil: insoluble	Disperses in water	(200)
Diester of castor oil fatty acid........		Ethanol, acetone, toluene: soluble Naphtha, mineral oil: insoluble	Disperses in water	(200)
Dodecaethylene glycol				
Monoester of coconut oil fatty acid ...	30–39	Ethanol, acetone, toluene: soluble Naphtha, mineral oil: insoluble	Dissolves colloidally in water	(200)
Diester of coconut oil fatty acid.......	30–39	Ethanol, acetone, toluene: soluble Naphtha, mineral oil: poorly soluble	Disperses in water	(200)
Monoester of commercial stearic acid..	36–37	Ethanol, acetone, toluene, naphtha: soluble Mineral oil: poorly soluble hot	Dissolves colloidally in hot water	(200)

Diester of commercial stearic acid	29–30	Ethanol, acetone, toluene, naphtha, mineral oil: soluble hot	Disperses in hot water	(200)
Monoester of commercial oleic acid	30–35	Ethanol, acetone, toluene: soluble Naphtha, mineral oil: insoluble	Dissolves colloidally or disperses in water	(200)
Diester of commercial oleic acid	25–35	Ethanol, acetone, toluene: soluble Naphtha: moderately soluble Mineral oil: poorly soluble	Disperses in water	(200)
Monoester of castor oil fatty acid	25–35	Ethanol, acetone, toluene: soluble Naphtha, mineral oil: insoluble	Dissolves colloidally in water	(200)
Diester of castor oil fatty acid	25–35	Ethanol, acetone, toluene: soluble Naphtha, mineral oil: insoluble	Disperses in water	(200)
Polyethylene glycol				
Diester of coconut oil fatty acid	53–54	Ethanol, toluene: soluble hot Acetone: moderately soluble hot Naphtha, mineral oil: insoluble	Soluble in water	(200)
Diester of commercial stearic acid	52–54	Ethanol, acetone, toluene: soluble hot Naphtha, mineral oil: insoluble	Soluble in water	(200)
(Di)ester of commercial oleic acid	50	Ethanol, acetone, toluene: soluble hot Naphtha, mineral oil: insoluble	Soluble in water	(200, 275, 488)
Diester of castor oil fatty acid	50	Ethanol, acetone, toluene: soluble hot Naphtha, mineral oil: insoluble	Soluble in water	(200)
Dioxanediol (2,3)				
Distearate	84			(510, 511)
Dioleate			Density, 0.904 (20°C.)	(510, 511)

TABLE 18

Glycerol esters: physical and chemical data

ESTER	MELTING POINT*	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
1-Monocaproate			Boiling point, 162°C. (4 mm. Hg)	(459)
1-Monocaprylate	40		Boiling point, 178–181°C. (5–6 mm. Hg) Refractive index, 1.4309 (85.7°C.) Density, 0.9646 (97.3°C.)	(450, 459)
1-Monocaprate	54; 53; 51.4; 51.2		Refractive index, 1.4331 (85.7°C.) Density, 0.9399 (97.3°C.) Conversion points of unstable forms: 49°; 27°; 8°C.	(20, 376, 450, 459)
2-Monocaprate	40.4		Refractive index, 1.44045 (70°C.)	(522)
1,3-Dicaprate	44.5	Ethanol: crystallizes in cold Light petroleum: gels	Conversion points of unstable forms: 42°; 37°C.	(377)
1-Monoundecoate	56.5		Conversion points of unstable forms: 52°; 36.5°; 3°C.	(376)
1,3-Diundecoate	49		Conversion points of unstable forms: 47°; 43.5°C.	(377)
1-Monolaurate	63.2; 63; 62–3; 62.5; 62; 61.5–62; 61; 60.5–61;	Ethanol (95%): soluble hot, crystallizes on cooling Ethanol (60%): soluble hot	Boiling point, 142°C. (green cathode light vacuum) Refractive index, 1.4350 (85.7°C.)	(20, 23, 35, 64a, 69, 171, 172, 176, 178, 179, 209,

	optically active, 53–4	Ether: (easily) soluble hot; soluble cold, crystallizes on cooling Benzene: poorly soluble Ligroin: crystallizes on cooling, poorly soluble cold Carbon tetrachloride, chloroform: soluble Acetone: easily soluble Carbon disulfide: crystallizes on cooling Ether–ligroin: crystallizes	Density, 0.9248 (97.3°C.) $[\alpha]_D$ of optically active *l*-form: −3.76° (in pyridine) Saponification value: 272.6, 204.2, 200.8, 207.0, 204.6, 204.5 Conversion points of unstable forms: 59.5°; 44(45)°; 15°C.	210, 259, 351, 376, 450, 459, 537, 550, 564)
2-Monolaurate	51.1		Refractive index, 1.4424 (70°C.)	(522)
1,3-Dilaurate	57; 56.6; 56.5; 56.3; 56; 55; 53	Ethanol (95%): soluble hot, crystallizes on cooling Ethanol (60%): insoluble hot, cold Ether: very soluble Petroleum naphthas: moderately soluble, crystallizes on cooling from ligroin, hexane	Saponification value: 236.4; 243.7; 243.2; 254.8; 250.5; 248.3; 259.8; 244.1 Molecular weight: 511.3, (233.8; 225.9), 517.4 Conversion points of unstable forms: 54°; 49.5°C.	(20, 172, 207, 208, 213, 377, 537, 538, 564)
1,3-Lauromyristate	34–5; 40–42			(209)
1,3-Laurostearate	45; 52–3			(209)
1-Monotridecoate	65		Conversion points of unstable forms: 61°; 50°; 9°C.	(376)
1,3-Ditridecoate	59.5	Ethanol: crystallizes on cooling Petroleum (light): crystallizes on cooling	Conversion points of unstable forms: 57°; 54.5°C.	(377)

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* Some of the very low, obviously untrustworthy melting points have been omitted, but references for them are entered.

TABLE 18—*Continued*

ESTER	MELTING POINT*	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
1-Monomyristate	70.5; 70; 69; 68; 67.9, 67.5	Ethanol: poorly soluble cold Ether: easily soluble, crystallizes on cooling Petroleum ether: crystallizes on cooling, poorly soluble Ligroin: poorly soluble Benzene: easily soluble Carbon disulfide: poorly soluble, crystallizes on cooling	Boiling point, 162°C. (green cathode light) Refractive index, 1.4366 (85.7°C.) Density, 0.9121 (97.3°C.) Saponification value: 187.8, 187.7 Conversion points of unstable forms: 67.5°; 56°(57°); 39.5°; 24°(27°)C.	(5, 20, 47, 48, 64a, 104, 172, 212, 323, 351, 364, 376, 450, 459, 564)
2-Monomyristate	61		Refractive index, 1.4420 (70°C.)	(522)
1,3-Dimyristate	68; 65.5; 64.5; 64.4; 63.8; 63.5; 63; 62; 61; 60.5	Ethanol: soluble hot, crystallizes, poorly soluble cold Amyl alcohol: crystallizes on cooling Ether: easily soluble, crystallizes on cooling Benzene: easily soluble Hexane, ligroin: poorly soluble, crystallizes on cooling Chloroform: easily soluble, crystallizes on cooling Carbon disulfide: poorly soluble	Saponification value: 219.7; 218.6 Conversion points of unstable forms: 63°; 60°C.	(20, 172, 207, 208, 212, 252, 323, 364, 377, 564)
1,2-Dimyristate	59			(122)

1,3-Myristostearate	58; 52–3	Ethanol: poorly soluble Ether, chloroform: soluble Carbon disulfide, ligroin: poorly soluble Benzene: soluble		(212)
1,3-Myristolinoleate	38; 15	Ethanol, methanol, ligroin, carbon disulfide: poorly soluble Benzene, ether, chloroform: (easily) soluble		(322)
1,3-Myristoricinoleate	33; 15			(322)
1-Monopentadecoate	72		Conversion points of unstable forms: 69°; 62°; 17°C.	(376)
1,3-Dipentadecoate	68.5	Hexane: crystallizes Hexane–benzene: crystallizes	Conversion points of unstable forms: 66.5°; 63.5°C.	(377)
1-Monopalmitate	78–9; 77.6; 77; 76; 75–75.5; 74–5; 71; optically active, 71–2	Ethanol, in grams per 100 g.: 4.1351 (21°C.); 5.3060 (22°C.); 4.09 g. per 100 cc. (25°C.); crystallizes; poorly soluble cold Methanol, isobutanol: crystallizes Acetone: crystallizes Ether: 2.75 g. per 100 cc. (25°C.); crystallizes Light petroleum: poorly soluble Benzene: crystallizes Pentane, chloroform: soluble	Boiling point, 190°C. (0.1 mm. Hg) Molecular weight, 325–6 Refractive index, 1.4484 (85.7°C.) Density: 0.9014 (97.3°C.); 1.04 g. per cubic centimeter Saponification value: 171, 186, 170, 172, 167.7 Optical rotation of *l*-form: $[\alpha]_D = -4.37°$ (in pyridine) Conversion points of unstable forms: 74°; 65°(66°); 34°C.	(5, 7, 8, 8a, 20, 23, 28, 38, 39, 44, 66, 75, 89, 97, 104, 121a, 122, 171, 176, 178, 179, 210, 225, 259, 351, 376, 383, 447, 450, 459, 561, 564)

TABLE 18—*Continued*

ESTER	MELTING POINT*	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
2-Monopalmitate	69.5; 69; 68.5; 68	Ethanol: 4.61 g. per 100 cc. (25°C.); moderately soluble, crystallizes Methanol: moderately soluble Ether: easily soluble hot, crystallizes on cooling; 11.15 g. per 100 cc. (25°C.) Ligroin: soluble hot Petroleum ether: poorly soluble hot Benzene: easily soluble hot, crystallizes Chloroform: easily soluble Acetone: moderately soluble Ethyl acetate: easily soluble hot	Refractive index, 1.44605 (70°C.) Molecular weight, 323	(36, 104, 121a, 122, 123, 522)
1,3-Dipalmitate	73; 72.5; 72; 70; 69.5; 69; 68.5	Ethanol, in grams per 100 g.: 0.2097 (20°C.); 0.5040 (27°C.); soluble hot, crystallizes on cooling Ether: easily soluble Ether, hexane, ligroin, petroleum ether: crystallizes Chloroform: soluble, crystallizes	Saponification value: 199, 198, 193.3, 194.3, 195.4, 197.6, 196.6 Acetyl saponification value, 239.9 Conversion points of unstable forms: 68°C.	(7, 8, 20, 37, 38, 39, 44, 75, 97, 172, 191, 206, 214, 225, 252, 377, 378, 383, 520, 564)

1,2-Dipalmitate	64; optically active, 67–67.5		Optically active (*d*) form: $[\alpha]_D = -2.3°$ (in $CHCl_3$)	(122, 512)
1,3-Palmitostearate	73.4; 71–71.3	Ether: crystallizes on cooling		(191, 550)
2,3-Palmitostearate	68.5–69.5			(554)
1,2-Palmitostearate	60.5–61			(554)
1-Monomargarate (heptadecoate)	77; 76.4; 75.7	Ethanol, in grams per 100 g.: 0.3015 (0°C.), 0.1015 (0°C.), 1.0545 (15°C.); 0.2650 (15°C.) Butanol: easily soluble Ethyl acetate, acetone: soluble Ether, in grams per 100 g.: 0.1945; 0.0725 (0°C.); 0.7810; 0.2499 (15°C.); poorly soluble cold Benzene: easily soluble Petroleum ether: easily soluble Chloroform, carbon tetrachloride: soluble	Refractive index: 1.4412, 1.4413 (80°C.) Saponification value: 161.1, 164.6 Conversion points of unstable forms: 74.5°; 70°; 28°C.	(378, 539)
1,3-Dimargarate (heptadecoate)	74.5; 71.8; 70.1	Ethanol, in grams per 100 g.: 0.0010; 0.0075 (0°C.); 0.0210; 0.0445 (15°C.) Ethyl acetate, acetone: easily soluble hot Ether, in grams per 100 g.: 0.0565; 0.0745 (0°C.); 0.5150; 0.7435 (15°C.) Petroleum ether, carbon tetrachloride, chloroform: easily soluble	Refractive index: 1.4407, 1.4404 (75°C.) Saponification value: 188.2, 186.0 Conversion points of unstable forms: 71.5°C.	(377, 539)

TABLE 18—*Continued*

ESTER	MELTING POINT* °C.	SOLUBILITY	OTHER INFORMATION	REFERENCES
1-Monostearate	83.5; 82; 81.5; 81–81.5; 81–2; 80; 80.9; 79.5–80; optically active, 76–7	Ethanol: moderately soluble hot, crystallizes Methanol, isobutanol: crystallizes Ether: easily soluble hot, poorly soluble cold, crystallizes on cooling Benzene: crystallizes on cooling Petroleum ether: very poorly soluble cold, crystallizes	Boiling point, 260°C. (12 mm. Hg), decomposes; volatile *in vacuo* Refractive index, 1.4400 (85.7°C.) Density, 0.8959 (97.3°C.) Saponification value: 156, 173.2, 155, 149.2, 156.5, 158; (74, 79.88, 75% stearic acid) Molecular weight: 358, 353–4 *l*-Form: optical rotation, $[\alpha]_D$ = −3.58° (in pyridine) Conversion points of unstable forms: 79°; 74°; 47.5°; 42°C.	(8, 20, 23, 28, 35, 38, 39, 44, 48, 89, 176, 178, 179, 208, 217, 219, 221, 225, 252, 253, 259, 260, 264, 314, 351, 370, 376, 450, 550, 564)
2-Monostearate	74.4		Refractive index, 1.44770 (70°C.)	(522)
1,3-Distearate	79.5–80; 79.5; 79.1; 78.5–79.1; 78.5; 77.5–78.2; 78; 77.5; 76.5; 76	Ethanol: poorly soluble hot (1:150); crystallizes Ether: soluble hot, poorly soluble cold Benzene, petroleum ether (ligroin), chloroform, hexane: crystallizes	Molecular weight, 625 Saponification value: 180, 181, 180.6; 186.5; 179.7; 187.2; 179.8; 181.8; 183, 181, 179.3; 180.2; (90.9; 91% stearic acid) Acetyl saponification value, 224 Hehner value, 92.3% Conversion points of unstable forms: 74°C.	(8, 20, 38, 39, 44, 64, 172, 177, 206, 207, 208, 211, 214, 217, 218, 219, 225, 252, 264, 352, 353, 370, 377, 378, 420, 449, 459, 549, 564)
1,2-Distearate	68.5–69; optically active, 74.5–75		*d*-Form: optical rotation, $[\alpha]_D$ = −2.7° (in $CHCl_3$, C., 6.18)	(512, 554)

1-Monoarach(id)ate (eicosanate).		Ether: very poorly soluble cold		(42)
1,3-Diarach(id)ate (eicosanate)..	75	Ether: very poorly soluble cold, poorly soluble hot Chloroform: easily soluble Carbon disulfide: soluble	Saponification value, 166.34	(42, 206)
1-Monocerotate.................	78.8	Ethanol: soluble hot Benzene: crystallizes		(379)
1,3-Dicerotate..................	79.5	Ethanol: very poorly soluble Ether: poorly soluble Benzene: easily soluble hot		(379)
1-Monomelissate................	91.5–92	Ethanol: soluble hot		(379)
1,3-Dimelissate.................	93	Benzene: soluble hot		(379)
1-Monoöleate..................	Freezes, 0, −6 Melts, 10 Crystallizes on standing. 35–40; 35; 26–27; 23.8–26; 23; 22	Ethanol (90%): soluble 100% Ethanol (80%): soluble 98.2% Ethanol (50%): soluble 97.6% Ethanol (80%): crystallizes Ethyl acetate: soluble 45.4% Acetone: soluble 49.2% Acetone (80%): soluble 100% Acetone (50%): soluble 88.3% Ether: soluble 92.6% Benzene: soluble 98.8% Petroleum ether: soluble 100%, crystallizes on cooling Chloroform: soluble 100% Carbon disulfide: soluble 89.2%	Boiling point: 300°C., decomposes (15 mm.); 238–240°C. (3–4 mm. Hg) Refractive index, 1.4605 Density, 0.947 (21°C.) Saponification value: 157.1, 181.8, 176.7, 159, 157 Molecular weight, 353.5–354 Iodine value: 70.1, 69.4, 70.6, 73.4, 67.22, 68.5	(8, 8a, 11, 13, 28, 38, 39, 44, 89, 155, 156, 225, 259, 260, 314, 325a, 335, 351, 370, 464, 533)

TABLE 18—*Continued*

ESTER	MELTING POINT* °C.	SOLUBILITY	OTHER INFORMATION	REFERENCES
1,3-Dioleate	14–16; crystallizes on storage at 15 or less	Ethanol (100%): soluble 90% Ethanol (80%): soluble 87.5% Ethanol (50%): soluble 74.2% Ether: soluble 100% Benzene, petroleum ether, chloroform, carbon disulfide, ethyl acetate: soluble 100% Acetone (anhydrous): soluble 100% Acetone (80%): soluble 75.4% Acetone (50%): soluble 74.2%	Refractive index, 1.4661 Density, 0.921 (21°C.) Saponification value: 182, 183 Iodine value: 80.4; 80.5 Molecular weight, 621	(13, 38, 39, 44, 225, 335, 370)
1-Mono-10,11-isoöleate	49			(65)
Monoelaidate	44.8	Ethanol: crystallizes Ether: very soluble Petroleum ether, chloroform, acetone: very soluble		(66)
1-Monobehenolate	50.5	Ethanol: crystallizes	Saponification value, 139 Iodine value, 61.6	(441)
1,3-Dibehenolate	42.5; 43	Ethanol: crystallizes Ligroin: crystallizes	Saponification value, 156.1 Iodine value, 68.9	(441)
1-Monostearolate	40.5; 40	Ethanol: poorly soluble cold, crystallizes Benzene, ligroin, chloroform: easily soluble	Saponification value, 160 Iodine value, 71.49	(441)

1,3-Distearolate	40; 38.5; 38	Ethanol: poorly soluble cold Ether, benzene, ligroin, petroleum ether, chloroform: easily soluble	Saponification value, 181.6 Iodine value, 82.31	(441)
Dierucate	47	Ethanol: poorly soluble cold, poorly soluble hot Ether, ligroin: easily soluble		(448, 523)
Dibrassidate	65; 67	Ether: poorly soluble		(448, 523)
1-Monolinoleate	14–15; crystallizes only at very low temperatures (−10, −26)	Ethanol, methanol: poorly soluble Ligroin, carbon disulfide: poorly soluble Ether, benzene, chloroform: easily soluble Ether, petroleum ether: crystallizes	Refractive index, 1.4758 Saponification value, 158.5 Iodine value, 142.1	(52, 322)
1,3-Dilinoleate		Ethanol, methanol, ligroin, carbon disulfide: poorly soluble Ether, benzene, chloroform: easily soluble	Saponification value, 180.3 Iodine value, 157.1	(216, 322)
1,3-Linoleoricinoleate				(322)
1-Monoricinoleate	Viscous at −15	Ethanol, methanol, ether, benzene, chloroform: easily soluble Ligroin, carbon disulfide: soluble		(322)
1,3-Diricinoleate		Ethanol, methanol, ether, benzene, chloroform: easily soluble Ligroin, carbon disulfide: soluble		(322)

ESTER	MELTING POINT*	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
Monoester coconut fatty acid....	40.8; 37.2		Saponification value: 186.5, 227.9, 220.5, 197 Hydroxyl value: 190.5, 244.4	(153, 336, 425, 427, 434)
"Monostearate," commercial.....	61.6; 59		Saponification value: 157, 170.4 Acetyl value, 159.6	(156, 200, 336)
"Distearate," commercial.......	54.5			(157)
Monoester olive oil fatty acid....	Crystallizes on storage		Saponification value, 181.8	(404)
Monoester cottonseed fatty acid..			Saponification value, 152 Acetyl value, 145	(152, 425, 471)
Diester cottonseed oil fatty acid..			Acetyl value, 263.5	(10)
Diester sesame oil fatty acid.....			Oleic acid, 86.41%	(10)
Monoester linseed fatty acid.....			Refractive index: 1.4788; 1.4785 (20°C.) Density: 0.988 (15.5°C.); 0.9818 (30°/15.5°C.) Saponification value: 168, 156.7, 184.9, 162.4, 166 Acetyl value: 156.2, 174.6, 157, 288 Acetyl saponification value: 300.3, 311 Molecular weight: 344.7, 354	(57, 73, 370, 391, 499)

		Refractive index: 1.4811; 1.4777 (20°C.) Density, 0.9314 (30°/15.5°C.) Saponification value: 183.3; 184 Molecular weight, 617 Hydroxyl value: 75; 81.2	(46, 73, 370)
		Saponification value, 176.4 Molecular weight, 318.8 Acetyl saponification value, 310.7	(391, 499)
		Refractive index, 1.4996 (20°C.) Density, 0.9934 (27°/15.5°C.) Saponification value, 161 Acetyl value, 308	(73)
		Refractive index, 1.5000 (20°C.) Density, 0.9718 (27°/15.5°C.) Saponification value, 182 Acetyl value, 83.3	(73)
		Saponification value: 183.9; 149.5 Acetyl value: 91; 191.2	(336)

TABLE 19

Esters of polyglycerol and glycerol ethers: physical and chemical data

ESTER	MELTING POINT	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
Glycerol trihydroxyethyl ether				
Monolaurate		Water: soluble		(295)
Monoöleate		Water: colloidally soluble		(275, 488)
Diglycerol				
Monostearate	About 30	Water: disperses Ethanol: soluble hot, crystallizes on cooling Ether: easily soluble	Saponification value (% stearic acid): 65.96 65.88	(264)
Distearate	70.5–71.3	Ether: very soluble Petroleum ether–ether: crystallizes on cooling		(221)
Polyglycerol				
Monoester of commercial stearic acid		Water: disperses	Saponification value, 152 Hydroxyl value, 284	(147, 432)
Monoester of lard fatty acid			Saponification value, 143 Iodine value, 31.6	(62)
Monoester of commercial oleic acid			Saponification value, 151 Iodine value, 69.4	(62)
Monoester of linseed oil fatty acid			Saponification value, 137.2 Iodine value, 116.7	(62)

E. SPECIFIC HEAT AND HEAT OF COMBUSTION

The heat of combustion for 1-monopalmitin was found to be 2778.78 ±0.36 kcal. per mole, and 2788.30 ±0.67 kcal. per mole for 2-monopalmitin. This indicates that conversion from the 2- to the 1-monoglyceride liberates 9.52 kcal. per mole. The heat of combustion calculated for 1-monomyristin is 2464 ±0.59 kcal. per mole (104).

TABLE 20

Erythritol and pentaerythritol esters: physical and chemical data

ESTER	MELTING POINT	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
Erythritol				
Dipalmitate....	99.5–101		Consists of 85% dipalmitate and 15% monopalmitate	(477)
Tripalmitate....	81–83		Consists of 72% tripalmitate and 28% tetrapalmitate	(477)
Mixed tri–tetrapalmitate.....	80–83		Consists of 57% tripalmitate and 43% tetrapalmitate	(477)
Mixed di–tristearate......	62–64.5		Consists of 36% distearate and 64% tristearate	(40, 477)
Tetraoleate.....			Iodine value, 85.6 Refractive index, 1.4540 (70°C.)	(518)
Pentaerythritol				
Tetrapalmitate.	70–70.5	Ethanol: soluble hot, crystallizes on cooling Benzene–ethanol: crystallizes	Stearic acid: 94.15; 94.18	(3)
Oleate..........			Saponification value: 197.9, 204.1 Iodine value, 73.8 Molecular weight, 1102; calculated, 1184	(53)
Erucate........			Saponification value, 209.9 Iodine value, 96.1 Molecular weight, 1609; calculated, 1416	(53)
Ester of linseed fatty acid....			Saponification value: 257.1, 212.3 Iodine value: 101.2, 122.1 Refractive index, 1.4900 Molecular weight, 320	(14, 139, 143)

TABLE 21

Pentose and methyl glucoside esters: physical and chemical data

ESTER	MELTING POINT	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
l-Arabinose				
Tetrapalmitate	69.5	Ethanol: poorly soluble Ether, acetone: moderately soluble Ethyl acetate: poorly soluble Chloroform, benzene: easily soluble	$[\alpha]_D^{18} = +4.24°$	(406)
α-Methyl-*d*-glucoside				
Tripalmitate	77	Ethanol: moderately soluble hot Ether, acetone: soluble in boiling solvent Ethyl acetate: moderately soluble Chloroform, benzene: very soluble		(405a)
Tetrapalmitate	69	Ethanol: poorly soluble Ether, acetone: moderately soluble hot Chloroform, benzene: easily soluble Carbon disulfide, ligroin: poorly soluble	$[\alpha]_D^{15} = +38.22°$ $[\alpha]_D^{18} = +46.9°$	(406)
Tristearate	82	Ethanol, methanol: poorly soluble Acetone: moderately soluble hot Ether, ethyl acetate; moderately soluble Chloroform, benzene: very soluble		(405a)
Tetrastearate	68	Ethanol, methanol: poorly soluble Acetone: moderately soluble hot Ether, ethyl acetate: moderately soluble Chloroform, benzene: very soluble		(405a)
Monoester of olive oil fatty acid			1-Methoxy-5,6-anhydroglucose-3-oleate	(318)

The molecular heat of combustion with constant pressure is 6979.5 kcal. for glycerol dierucate, and 6953.7 kcal. for glycerol dibrassidate; with constant volume, the values are 6968.2 kcal. and 6942.4 kcal., respectively (523).

The specific heats for the 1- and 2-monopalmitins at 25°C. are 0.436 ±0.001 and 0.439 ±0.001 cal. gram^{-1} degree^{-1}, respectively (104).

F. OPTICAL ROTATION

Many sugar and sugar alcohol esters are optically active (58, 59, 60, 61, 256, 406, 565). All other asymmetric polyhydric alcohol esters are theoretically capable of optical rotation. However, sufficiently well defined pure optical isomerides of the glycerides were obtained only recently. Thus levorotatory 1-monoglycerides (23, 178, 179) and dextrorotatory 1,2-glycerides (512) have been prepared.

G. FLU ORESCENCE

Many polyhydric alcohol esters of fatty acids are strongly fluorescent. Certain commercial esters of glycol, diethylene glycol, polyglycol, glycerol, mannitol, and sorbitol, under radiation of 3650 Å., showed fluorescence varying from blue to green, and from yellow to brown (128a).

H. SURFACE TENSION

The surface tensions (in dynes per centimeter at 97.3°C.) of the 1-monoglycerides have been determined (450) by Sugden's maximum bubble pressure method:

ESTER	SURFACE TENSION	ESTER	SURFACE TENSION
Monocaprylin	26.69	Monomyristin	24.88
Monocaprin	25.43	Monopalmitin	25.54
Monolaurin	25.28	Monostearin	25.07

The surface tension of monolaurin is considerably lower than that of dilaurin and of trilaurin; the interfacial tensions of dilaurin and of trilaurin against alkaline solutions are much lower than against neutral or acid solutions (542a).

Surface action on paraffin and contact angles of glycol diesters have been measured (398a).

I. PARACHOR

The parachor was calculated for the 1-monoglycerides from their surface tension and density, and is given here together with the corresponding theoretical values (450):

ESTERS	PARACHOR		ESTERS	PARACHOR	
	Found	Calculated		Found	Calculated
Monocaprylin	514	529	Monomyristin	740	763
Monocaprin	588	607	Monopalmitin	823	841
Monolaurin	664	685	Monostearin	894	919

TABLE 22

Hexitol, hexitan, and hexide esters: physical and chemical data

ESTER	MELTING POINT	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
Mannitan dilaurate.....	122	Water: insoluble Ethanol, methanol: poorly soluble cold Ether: easily soluble cold, soluble hot Benzene: soluble hot, poorly soluble cold Chloroform: poorly soluble Acetone: poorly soluble	$[\alpha]_D = +8.5°$ (CHCl$_3$) Lauric acid: 75.68, 75.79% Density, above 1	(61, 323)
Isomannide dilaurate...	37.5	Ethanol: very soluble cold Ether: very soluble Benzene: soluble cold Chloroform: soluble	Volatilizes slowly *in vacuo* with decomposition Optical rotation, strongly dextrorotatory Refractive index: 1.4570 (40°C.); 1.4500 (60°C.)	(61)
Mannitan dimyristate...		Water: insoluble Ethanol, methanol: poorly soluble cold Ether, benzene, chloroform: soluble Acetone: poorly soluble cold		(323)
Mannitan dipalmitate..		Water: insoluble Ethanol, methanol: poorly soluble cold Ether, benzene, chloroform: soluble Acetone: poorly soluble	Volatilizes *in vacuo*	(42, 323)
Mannitol hexapalmitate.	64.5	Ethanol: poorly soluble hot, cold Ether: easily soluble Petroleum ether, chloroform: easily soluble Ethyl acetate: easily soluble, crystallizes	Palmitic acid: 95.06%	(521)

Mannitan distearate....	116.5; 124; 67–72	Water: insoluble Ethanol: soluble hot, poorly soluble cold (crystallizes) Ether: soluble hot, very poorly soluble cold Benzene: soluble hot, very poorly soluble cold Naphtha: soluble hot Chloroform: 5% soluble, very poorly soluble cold Acetone: poorly soluble (crystallizes) Ethyl acetate: soluble hot	Volatile *in vacuo* Stearic acid: 81.64, 81.45, 80.91, 82.44% $[\alpha]_D^{16} = +8.0°$ ($CHCl_3$) Molecular weight, 704–706.6	(42, 59, 323, 354)
Mannide distearate.....	51	Water: insoluble Ethanol, methanol: very soluble hot, very poorly soluble cold, crystallizes Ether: crystallizes Benzene, chloroform: soluble	Stearic acid: 84.8% $[\alpha]_D^{20} = +63.9°; 64.9°$ Molecular weight, 706 Density, above 1 Semi-translucent, brittle, white solid; conchoidal fracture	(58)
Isomannide stearate...	61.5	Ethanol: easily soluble hot, crystallizes Ether: easily soluble cold Benzene, chloroform: easily soluble cold	Volatile *in vacuo* $[\alpha]_D^{20} = +93.63°$ Molecular weight, 667 Amorphous, waxlike	(59)
Mannitol stearate......			Saponification value, 154.3 Molecular weight, 1766; theoretical, 1778	(53)
Mannitan dioleate (olive fatty acid)...........		Ether: easily soluble	Volatile *in vacuo* Structural formula: 3,6-dehydro-4,5-oleyl mannitol	(41, 319, 354)
Isomannide dioleate....			Oleic acid: 83.65%	(354)

TABLE 22—*Continued*

ESTER	MELTING POINT	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
Mannitol oleate			Saponification value: 248.6, 182.5 Iodine value: 92.9, 76.4 Molecular weight: 727.3, 1625	(139)
Mannitol erucate			Saponification value, 162.4 Iodine value, 78.4 Molecular weight, 1215; theoretical, 2102	(53)
Mannitol ricinoleate			Saponification value: 172.2, 160.6 Iodine value: 69.8, 89.4 Molecular weight: 1407, 1866; theoretical, 1862	(139)
Mannitan monoester of coconut oil fatty acid	15–20 (setting point)	Ethanol: soluble Toluene: soluble Benzene, mineral oil: soluble Chlorinated solvents: soluble Ether-alcohols: soluble Ketones: soluble	Density, 1.02 Refractive index, 1.475 (25°C.)	(572)
Mannitan monoester of commercial stearic acid	45–55 (setting point)	Ethanol, ether-alcohols: soluble Esters: poorly soluble hot Chlorinated solvents, hydrocarbons: poorly soluble Castor oil: soluble Oils: soluble (hazy)	Density, 1.02	(572)

Mannitan monoester of commercial oleic acid.	10–15 (setting point)	Ethanol: soluble Methanol: poorly soluble Hydrocarbons, chlorinated solvents: soluble Ketones, ether-alcohols: soluble Esters, oils: poorly soluble	Density, 1.02 Refractive index, 1.485 (25°C.)	(572)
Mannitol diester of linseed oil fatty acid....			Molecular weight, 706 Refractive index, 1.4880	(370)
Mannitol tetraester of linseed oil fatty acid..			Saponification value: 259, 227, 159.9, 181.5 Iodine value: 98.1, 91.8 Molecular weight: 1120, 1230 Refractive index, 1.4880	(139, 370)
Sorbitan monolaurate...		Water: emulsifies	Waxlike	(274, 288, 487)
Sorbitan Monoester of coconut oil fatty acid.......	14–16 (setting point)	Ethanol: soluble Ether: moderately soluble Benzene: moderately soluble Chlorinated solvents: soluble Ether-alcohols: soluble Amines: soluble Ketones, esters, oils: moderately soluble	Saponification value, 160–170 pH (dispersion), 6–7 Density, 1.02 Refractive index, 1.472 (25°C.)	(572)

TABLE 22—*Concluded*

ESTER	MELTING POINT	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C			
Monoester of commercial stearic acid....	45–55	Ethanol: soluble hot Ether: poorly soluble Benzene: soluble Petroleum ether: poorly soluble Chlorinated solvents: soluble Esters, ketones, ether-alcohols: poorly soluble	Density, 1.02	(572)
Monoester of commercial oleic acid......	5–6	Alcohol, ether, chlorinated solvents: soluble Esters: poorly soluble Oils: soluble	Saponification value, 135–140 pH (dispersion), 6–7 Surface tension (in 1 per cent aqueous solution), 27.5 dynes per cm^2.; (in 0.01 per cent), 31.2 dynes per cm.^{2} Density, 1.02	(572)
Dulcitol				
Hexapalmitate.......	74	Ethanol: poorly soluble Ether: moderately soluble hot Chloroform: easily soluble Benzene, pyridine, carbon disulfide: moderately soluble Acetic acid, ligroin: poorly soluble	Amorphous	(406)
Sorbitol hexahydroxyethyl ether				
Monolaurate..........	*	Water: soluble		(274, 288, 487)
Hexalaurate..........		Ethanol: easily soluble Acetone: soluble		(304)

J. VISCOSITY

The viscosity of a number of polyhydric alcohol esters has been determined. The values for certain monoglycerides are: monocaprylin, 0.0603; monocaprin, 0.0772; monolaurin, 0.0983; monomyristin, 0.1210; monopalmitin, 0.1472; monostearin, 0.1691 poises, at 97.3°C. (450). For certain ethylene glycol esters the values at 25°C. are: dioleate, 0.28; dilinoleate, 0.22; dilinolenate, 0.10 poises (414).

A number of viscosity determinations have been made for the esters of mixed fatty acids of certain oils (14, 73, 258, 499, 566, 572). Thus, for the glycol mono-, glycerol mono-, glycerol di-, and pentaerythritol esters of linseed oil fatty acids it is 0.5, 1.4, 0.6, 1.4 poises, respectively, at 25°C.; for the glycol monoester and the glycerol mono- and di-esters of tung oil fatty acids it is 2.25, 36.2, and 63.3 poises at 25°C.; for the glycerol monoester of dehydrated castor oil fatty acids it is 60 poises at 25°C. The sorbitan and mannitan monoesters of coconut oil fatty acids have viscosities of 40–60, and 20–40 poises, respectively, and mannitan monoleate a viscosity of 25–45 poises at 25°C.

K. THIN FILMS; STRUCTURAL DATA FROM SURFACE TENSION AND X-RAY MEASUREMENTS, ETC.

Films of polyhydric alcohol esters on distilled water have been studied by means of the surface-tension balance and by x-ray methods. Data for glycol esters (2, 103a, 370), the glycerides (5, 7, 25a, 370, 376, 377, 520), pentaerythritol (3), mannitol (370), and glucose esters (401) have been recorded.

The molecular length (film thickness) ranges from 10.2–12.8 Å. (cm. × 10^{-8}) for the linseed oil fatty acid esters of glycol (diester), diethylene glycol (diester), glycerol (monoester, diester), and mannitol (diester, tetraester), and for glycerol mono- and di-oleates. It is 24 Å. for dipalmitin, 20.6 Å. for monostearin, and 21.3 Å for distearin.

The molecular cross section is 22 Å. for glycol dipalmitate.

The molecular area has been measured when the film is "expanded", is under "no compression", and is at the "crumpling point" (all in square Ångström units or $cm.^2 \times 10^{-16}$):

ESTER	EXPANDED	NO COMPRESSION	CRUMPLING POINT
Glycol distearate		49.5; 51	
Glycol dilinseed		98	72
Glycol diricinoleate		253	
Diethylene glycol dilinseed		110	73
Glycerol monomyristate	70	26.3	
Glycerol monopalmitate	65; 70	26.3	
Glycerol dipalmitate		46; 46.4; 44.7	
Glycerol monostearate		27	20
Glycerol distearate		49	41
Glycerol monoöleate		47	25
Glycerol dioleate		86	63
Glycerol monolinseed		61	35
Glycerol dilinseed		103	73
Pentaerythritol tetrapalmitate		100	80
Mannitol dilinseed		105	75
Mannitol tetralinseed		176	147

TABLE 23

Sugar esters: physical and chemical data

ESTER	MELTING POINT °C.	SOLUBILITY	OTHER INFORMATION	REFERENCES
Glucose monolaurate....	110	Water: colloidally soluble Ethanol: easily soluble hot, poorly soluble cold Ether: easily soluble hot, poorly soluble cold	Specific rotation, 30° Reduces Fehling's solution	(60)
α-Glucose dilaurate.....	55	Water: colloidally soluble Ethanol: soluble hot, crystallizes on cooling Ether: poorly soluble cold	Specific rotation, 21.8° Reduces Fehling's solution	(60)
β-Glucose dilaurate.....	33	Water: colloidally soluble Ethanol: soluble hot, poorly soluble cold Ether: soluble cold	Specific rotation, 30° Reduces Fehling's solution	(60)
α-Glucose pentalaurate..	52	Ethanol: poorly soluble cold Ether, petroleum ether, chloroform: easily soluble Acetone, ethyl acetate: easily soluble hot Benzene, carbon disulfide: easily soluble	$[\alpha]_D^{20} = 40.62°$ ($CHCl_3$)	(565)
β-Glucose pentalaurate..	66	Ethanol: poorly soluble cold Ether, benzene, petroleum ether, chloroform, carbon disulfide: easily soluble Acetone, ethyl acetate: easily soluble hot	$[\alpha]_D^{20} = +3.9°$ ($CHCl_3$)	(565)
α-Glucose pentapalmitate..................	72-75	Ethanol: poorly soluble Ether, petroleum ether, chloroform: easily soluble Acetone, ethyl acetate: easily soluble hot	$[\alpha]_D^{20} = +29.7°$ ($CHCl_3$)	(565)

β-Glucose pentapalmitate	68–72	Ethanol: poorly soluble Ether, benzene, petroleum ether, chloroform, carbon disulfide: easily soluble	$[\alpha]_D^{20} = +4.6°$ ($CHCl_3$)	(565)
Glucose pentapalmitate	65–67; 62	Ethanol: gels on cooling Ether, benzene, chloroform, petroleum ether: easily soluble Ethyl acetate: crystallizes on cooling	$[\alpha]_D^{16} = +34.30°$	(256, 521)
Glucose Monostearate	110; 56.5–57	Water: colloidally soluble Ethanol, methanol: poorly soluble cold, crystallizes Ether: easily soluble, poorly soluble cold Mineral oil, acetone: soluble hot Benzene, chloroform: easily soluble	Specific rotation, 36.25° Reduces Fehling's solution	(60, 484)
Distearate	90–95	Water: colloidally soluble Ethanol: soluble hot, crystallizes, poorly soluble cold Ether: soluble hot, poorly soluble cold	Dextrorotatory Reduces Fehling's solution	(60)
Tristearate	60	Ethanol: soluble hot, poorly soluble cold Ether: soluble cold	Specific rotation, 12.00° Reduces Fehling's solution	(60)
Pentastearate	72–78; 70–71	Ethanol, methanol: poorly soluble cold Ether, petroleum ether, acetone, ethyl acetate: easily soluble hot, poorly soluble cold	$[\alpha]_D^{20} = +14.12°$ ($CHCl_3$) $[\alpha]_D^{16} = +34.17°$	(256, 565)
Stearate		Water: colloidally soluble Ethanol (absolute): soluble Ether: very soluble	Reduces Fehling's solution	(43)
Pentaoleate		"As for triolein"	$[\alpha]_D^{16} = +27.51°$	(256)

TABLE 23—*Concluded*

ESTER	MELTING POINT	SOLUBILITY	OTHER INFORMATION	REFERENCES
	°C.			
Glucose—(*Cont'd*)				
Ester of coconut oil fatty acid	41	Water: colloidally soluble Ether: soluble cold	Specific rotation, 21° Reduces Fehling's solution	(60)
Sucrose				
Octapalmitate	54–55	Ethanol: crystallizes Petroleum ether: crystallizes	$[\alpha]_D^{18} = +17.12°$	(256)
Octastearate	57	"As for tristearin"	$[\alpha]_D^{18} = +16.55°$	(256)
Linoleate		Benzene, turpentine, oils: soluble	Limpid viscous oil	(25, 265, 292, 465)
Eleostearate		Hydrocarbons, turpentine: soluble		(292)
Raffinose				
Hendecapalmitate	52–53; 43; 47	Alcohol, acetone: poorly soluble Ether: moderately soluble hot Benzene, chloroform, ethyl acetate: easily soluble	$[\alpha]_D^{20} = +31.8°$; $+4.2°$; $+27.2°$ ($CHCl_3$)	(256, 406)
Hendecastearate	63	Alcohol, acetone: poorly soluble Ether: moderately soluble hot Benzene, chloroform, ethyl acetate: easily soluble	$[\alpha]_D^{20} = +28.3°$ ($CHCl_3$)	(256, 406)

These, as well as other data, such as viscosity in solution (514, 515), have been used for the interpretation of the molecular structures of these esters (2, 3, 5, 7, 7a, 376, 377, 520). Ethylene glycol esters were unsuccessfully studied for anisotropical behavior under stress (555). The problem of forming multilayers on solid surfaces from monolayers on water has also been studied (4, 520).

Differences in adsorption on solids, such as alumina or silica gel, have been used to separate monolycerides from diglycerides (334).

L. CHEMICAL BEHAVIOR OF THIN FILMS

The rate of hydrolysis of certain glycerides under the influence of sodium hydroxide is proportional to their emulsifiability (383). The activation energy against sodium hydroxide was found to be 15,000 cal. for monopalmitin and 20,000 cal. for dipalmitin (7). The action of potassium permanganate–sulfuric acid on a monolaurin film was negative (4).

M. PHYSIOLOGICAL DATA

The formation of glycerides and other polyhydric alcohol esters by the action of certain enzymes has been studied (lipase from pancreas or the castor bean; adipose tissue; cytoplasma enzyme; bile salts), but could not be covered here. Certain glycol esters have been investigated as activators for the male sex hormone, testosterone, but only 1,3-propanediol palmitates were found effective (408, 409).

The question of the use of various polyhydric alcohol esters for foods has also been studied. Results on the value and permissibility of certain glycol esters in foods are controversial (121, 182, 357, 384, 466). Monoglycerides and diglycerides are harmless, and are utilized in the body as easily as fats of corresponding melting points (11, 76, 416, 464). Similarly, polyglycerol esters have been found harmless (62). There is also no objection against the use of mannitan and glucose esters in foods (59, 60, 61, 354).

III. Industrial Uses of Polyhydric Alcohol Esters

The extensive patent literature covering the preparation and use of polyhydric alcohol esters testifies to the considerable interest these materials have aroused in industry. Most applications of the polyhydric alcohol esters in various industries can be traced back to certain fundamental properties of these esters. It has been pointed out earlier that there are two basic types of polyhydric alcohol esters: namely, the completely and the partially esterified polyhydric alcohols. The partially esterified polyhydric alcohols are by far the more important group, because of their peculiar position between the hydrophilic and lyophilic materials. As a consequence, esters of this group have found definite use as interface modifiers. The wide variety of materials allows them to be "tailored" into an interface-modifying chemical or compound for almost any purpose. The inclusion of the group of ethers of polyhydric alcohol esters has extended this variety even further, and some of the most valuable interface modifiers are derived from it. It should be noted that certain completely esterified polyhydric alcohol ethers also are valuable as interface modifiers. In this case the hydrophilic character is due to ether linkages, not to hydroxyl groups.

The uses of the polyhydric alcohol esters will be surveyed below as a function of certain of their basic properties.

Some polyhydric alcohol esters may be used to replace the natural fats and oils because of their higher melting points or lower freezing points.

Monoesters and diesters of glycol or of glycerol derived from medium-chain-length fatty acids may serve as low-freezing low-viscosity lubricants for precision instruments (508).

On the other hand, hexitols or monosaccharides, fully esterified with cocoa butter fatty acids, were recommended to replace up to 25 per cent of chocolate fat (cocoa butter), in order to raise the melting point of the latter and to prevent the blooming of the chocolate (154).

Certain glycol esters, particularly of Montan wax, are recommended to replace Japan wax (174) and Carnauba wax (481), and as ingredients of wax polishes (313).

Certain esters of glycol (158), propylene glycol (49, 50), hexitol, and pentaerythritol (503) are stated to replace cocoa butter in suppositories. They have been suggested for this purpose also because they absorb water or disperse in it.

Glycol ricinoleates, as well as glycerol mono- or di-ricinoleates, may replace castor oil in the preparation of hydraulic fluid compositions of lower freezing point (19, 134, 135, 556, 558, 562). Glycerol or glycol polyricinoleates may replace castor oil in lubricating oils in order to lower their freezing point and viscosity index (542). Glycol distearate (417), as well as mannitan or sorbitan tetrastearates (418), are added to lower the pour point and to increase the viscosity index of lubricating oils.

Other applications for the polyhydric alcohol esters are based on their modified compatibility, solubility, or solvent power.

Glycol stearate has been suggested as an embedding material for microtome slicing, where it is superior to paraffin, as it is more compatible with alcohol and with water (413).

Diglycerides can dissolve 25 per cent to 30 per cent of phosphatides, such as lecithin (165, 166).

Polyhydric alcohol esters, such as the monoesters of glycerol, polyglycerol, or diethylene glycol, may be used as vehicles for water-soluble dyes. The dye then becomes effective on contact with moisture, as in lipstick (18, 233). Diethylene glycol laurate serves as a solvent for aniline dyes. Combined with mineral oil, it forms a non-volatile, non-hygroscopic liquid, suitable for reproduction of copies, e.g., with the Hectograph (107). Diethylene glycol laurate and tricresyl phosphate, containing an aniline dye in solution and a pigment, constitute a ribbon ink used in forming lithographic images on non-metallic plates (394).

Glycerol and glycol polyricinoleates are more compatible with mineral oil than is castor oil (542). Glycol ricinoleates, glycerol monoricinoleate, and glycerol diricinoleate find use in hydraulic fluids and lubricants, being more compatible with alcoholic solvents than is castor oil (19, 134, 135, 556, 558, 562).

Glycerol or other polyhydric alcohol monoricinoleates serve as solvents for aluminum stearate to form grease bases (180). Blends of glycol or glycerol esters of solid fatty acids with metal soaps are useful waxes (131, 392a).

Monoglycerides dissolve or blend with many resins such as natural resins (390, 391, 392, 499), shellac (46, 390, 392), alkyds (141), phenol-formaldehyde resins (380, 462), or aminotriazine–aldehyde resins (9), at elevated temperatures. In many cases they also react, forming modified products. Melamine–urea–formaldehyde resins may be plasticized by diglycol laurate (125). Hydroxy fatty acid esters of polyhydric alcohols dissolve acrylic resins, forming valuable blends (132).

Certain glycol or glycerol esters may serve as ingredients of polishes, owing to their high "solvent-fixing" power (solvent retention) (273, 286, 439, 481). Glycol or glycerol esters in conjunction with metallic soaps also are useful for this purpose (439). Emulsion polishes may be prepared with glycol esters (192, 496). A 3 per cent solution of glucose monostearate in white mineral oil will gel on cooling (484).

Diethylene glycol mono- and di-laurates have been suggested for perfume fixation (94).

Certain esters of glycol (258, 566) and of polyglycols, such as diethylene, triethylene, or dipropylene glycols (125, 158, 339), as well as polyhydric alcohol (glycol, glycerol, ether-glycols, mannitol, polyglycerol, pentaerythritol) esters of monohydroxy- or polyhydroxy-fatty acids (87), are described as plasticizers for nitrocellulose. Glycol ricinoleate (16), and esters of polyethylene glycol with fatty acids which are selected to give a product with a boiling point of 300–400°C. (369), may serve to plasticize cellulosic materials. Dioxanediol esters also may be used as plasticizers (510, 511).

Compositions containing diethylene glycol esters of fatty acids are suggested for use with zein (51).

Diethylene glycol esters may be used to soften or plasticize rubber and chlorinated rubber (29, 158). Glycerol monoricinoleate has possibilities as a softener for butadiene-type synthetic rubber (125).

Fatty acid esters of glycerol, pentaerythritol, sorbitol, glucose, sugars, inositol, or quebrachitol (145, 294), of dioxanediol (510, 511), the partial esters of glycol and glycerol (192), diethylene glycol (29), and water-soluble esters of polymerized polyhydric alcohols (34) are suggested as plasticizers.

Monoglycerides inhibit crystallization in fatty materials, such as saturated higher alcohols, waxes, hydrogenated oils, or solid fatty acids (15). Very small amounts (0.02–0.25 per cent) of completely esterified polyglycerols lower the pour test of salad oils on chilling (148).

Polyhydric alcohol esters may also serve for a variety of coating purposes.

Mono- and di-glycerides are used to form coatings on certain hygroscopic water-soluble solids, such as bile salts, liver concentrates, meat extracts, or powdered fertilizers, and may act to prevent caking of these materials when they are stored as powders (12, 337).

Certain monoglycerides or glycol esters may be used as casein-resisting coatings for milk bottle paper caps (507).

The softening, fulling, and sizing of rayon can be accomplished by dispersions of polyhydric alcohol esters, for instance, by ethylene, butylene, or amylene glycol monoesters (305, 341), glycerol mono- or di-esters (305), diethylene glycol esters (77), and monoesters of erythritol, arabitol, mannitol, etc. Textile sizing in general may be carried out with monoesters of ethylene glycol (192, 496), diethylene glycol (29, 130, 146, 403), polyglycols (275, 278), and glycerol (146, 412a), but also with esters of polyglycerols, pentaerythritol, erythritol, hexitols, sugars, and of the hydroxyalkyl ethers of polyhydric alcohols (96, 274, 276, 288, 307, 402, 412b, 487). Pile fabrics may be stiffened with glycol or diethylene glycol esters (136). Twisted cellulose yarns may be sized by soap–glyceride emulsions (505).

Water-soluble polyglycol esters of fatty acids may be used to disperse long-chain alkyl biguanidines, useful as textile softeners (280).

Water-soluble esters of polymerized polyhydric alcohols are stated to form useful films or coatings (34).

Certain polyhydric alcohol esters, mixed with oils and emulsified in water, may act as leather lubricants (29, 275, 302, 496). Mono- and di-glycerides are said to improve the consistency and lubricating action of lubricating oils (535). Esters of glycol (496), diethylene glycol, triethylene glycol, and polyethylene glycol (146, 365), polyglycol (275, 302, 488), glycerol (146), hydroxyalkyl ethers of polyhydric alcohol (274, 288, 487), esters of sorbitol (273, 286), of glycerol, erythritol, or mannitol (203), and polyglycerol-glycerol (236) have been recommended as textile lubricants. They are applied dispersed in water, either by themselves or with the aid of an emulsifying agent such as soap.

The introduction of polyhydric alcohols other than glycerol into drying oils, accomplished either by esterification of drying oil fatty acids, or by alcoholysis of drying oils followed by reësterification, has given some interesting results.

Glycol esters of drying oil fatty acids (73, 139, 142, 290, 386, 404, 414, 424), propylene glycol esters (73, 139), and the mono- and di-glycerides of drying oil fatty acids (73, 301, 309, 390, 499) are either slow drying or do not dry at all. Pentaerythritol esters (14, 53, 55, 139, 140, 142, 143, 144, 145, 273, 286, 290, 294, 504) and hexitol esters (14, 53, 139, 143, 144, 273, 286, 294, 504) are generally faster drying and more heat convertible than the corresponding glyceride oils. Special drying oils may be obtained from inositol (145), quebrachitol (145, 315), or from trimethylolmethane (290). Sugar esters (25, 145, 265, 292, 294, 465) are said to dry even more quickly and to be converted into insoluble and infusible resinous materials by heat.

Gelation of tung oil during heat treatment can be relieved by addition of monoglyceride (534).

The partial fatty esters of polyhydric alcohols and of their ethers, as well as certain completely esterified polyhydric alcohol ethers, are able to modify the surfaces of aqueous solutions and the interfaces between water and another liquid not soluble in water, that is, to act as emulsifying, dispersing, wetting, anti-spattering, foaming, suspending, or stabilizing agents. The esters are ordinarily not used alone, but in conjunction with other surface-active agents. An analysis of a commercial ester (381) shows such a combination with soap. However, a number of polyhydric alcohol esters have become known which, by themselves, are sufficiently well balanced in their affinities both for water and for non-aqueous materials so as not to require any stabilizers (200).

Within the large group of polyhydric alcohol esters there are compounds which are most suited for a particular purpose, such as wetting, anti-spattering, dispersing, or emulsifying action. Naturally, the variety of problems involving the modification of interfaces is very large and to date there is no reliable way of predicting which ester will be best suited for a certain task. The usually wide and sweeping claims of patents dealing with this matter have complicated the situation further.

The ability of polyhydric alcohol esters to disperse (form milks) in water had been observed by a number of early investigators, who first described this property, e.g., for the monoglycerides (75, 103, 548), diglycerol monostearate (264), mannitol esters (323), and the glucose esters (43, 60, 484).

There are numerous uses for polyhydric alcohol esters dispersed in water. Dispersions of certain diethylene glycol esters are said to be suited as lubricants for the stamping and drawing of nickel alloys, tin, aluminum, brass, and similar alloys (125). Such lubricant films are stated to be easily fired off in annealing, and also to permit the stamping of lacquered metal without fracture of the coating.

The use of dispersed polyhydric alcohol esters for textile sizing, softening, and for lubrication has already been mentioned.

Diethylene glycol stearate, blended with paraffin and amorphous petroleum wax and emulsified in water, may be applied (by spraying) to aluminum surfaces, e.g., in refrigerators, to dry there and act as a protective coating (125); similarly, this may be used to protect iron surfaces.

Glycol stearate, together with dimethyl cellulose, may be used as a thickener in dentifrices (440). Glycerol monostearate together with Irish moss will thicken and stabilize dairy products (326). Glycol and glycerol monostearates, stabilized by wetting agents (e.g., lauryl sulfate, oleyl methyl aminomethane sulfate) may be used to thicken aqueous hair dyes (525, 526). Glycol, diethylene glycol, and triethylene glycol esters have been claimed to be "edible" thickeners for use in custards, etc. (32).

Glycerol monolaurate (30), laurates of diethylene glycol, triethylene glycol, propylene glycol, mannitol, sorbitol, erythritol (184), and combinations of diethylene glycol or glycerol esters with lecithin (500) may be added to yeast to improve its wrapping and cutting quality, to reduce its crumbliness, and to improve its whiteness.

Mono- and di-glycerides are added to improve the whipping properties of cream (421). Glycol, diglycol, and particularly glycerol mono- and di-esters improve ice cream formulation by controlling "over-run", that is, the amount of air whipped in (226, 388, 468). They may also be added to frozen confections similar to ice cream (360).

Mono- and di-glycerides (243a, 249, 395, 397, 531), polyglycerol esters, glycol esters, hexitol, and sugar esters (241, 250, 397) are added to frozen or powdered dried egg materials, to prevent leakage of moisture upon thawing and to improve their emulsifying power.

Polyethylene glycol ricinoleate is said to be useful in the preparation of "completely soluble" antigens from microörganisms (311). Unsuccessful attempts were made to use glycerol and mannitol esters for a similar purpose (322, 323).

Polyhydric alcohol esters may also serve as dispersing agents in non-aqueous media.

Esters of polyhydric alcohol ethers, such as diethylene glycol stearate, will stabilize the suspension of iron and nickel carbonyls in liquid hydrocarbon fuels, used as anti-detonating agents (438).

Pigment dispersions in paint or varnish vehicles are said to be stabilized by glycol monostearate (496), by polyglycerol esters (236), by diethylene glycol stearate (29), and by a combination of glycol esters and metallic soaps (385). A diethylene glycol laurate was found to act as a true dispersing agent in pigment grinding in linseed oil, while diethylene glycol oleate and linseed oil monoglyceride had no effect (129, 501).

Monoglycerides (329) and polyglycerol and diethylene glycol monoesters (240) will reduce the viscosity of chocolates (i.e., cocoa powder–cocoa butter pastes); candy confections, such as enrobing materials, icings, etc. are similarly affected. An addition of 10 per cent of mono- or di-glyceride will stabilize peanut butter against gravitational settling of the suspended nut solids (86).

Diethylene glycol stearate aids pigment suspension in ink (29) and acts as a "stabilizer" in phosphorescent inks (485).

Polyglycerol monoesters may be used to stabilize pigment dispersions for the dulling or delustering of textiles (96). Mannitol or diethylene glycol stearates may be used to incorporate metallic powders into paper pulp, in order to manufacture a conductive paper (342).

Glycerol monostearate dispersions have been suggested for the stabilization of pigment dispersions in latex (125).

Esters of polyalkylene glycols (199, 275, 278, 280, 379, 488), glycerol (412a), polyglycerol (63, 160, 161, 228, 236, 238, 276, 412a, 412b), hydroxyalkyl ethers of polyhydric alcohols (274, 288, 295, 308, 412b, 486, 487), and of erythritol, pentitols, hexitols, or sugars (288) have been named as dispersing agents. However, it must be said that, as a rule, this term has been used rather loosely and often refers to emulsifying power (the ability to stabilize a dispersion of a water-insoluble liquid in water) and not dispersing action (the ability to stabilize and thin dispersions of solids by neutralizing the mutual attraction of the dispersed particles).

Polyhydric alcohol esters may be used as wetting, spreading, penetrating, and levelling agents.

Glycol and diethylene glycol monoesters and also mono- or di-glycerides are used as depressants of interfacial tension, by dissolving them in sub-emulsifying quantities in the oil of certain therapeutic compositions (399).

Glycerol monolaurate (69, 349), esters of hydroxyalkyl ethers of polyhydric alcohols (527), sorbitol monoesters (528), and polyglycerol monoesters (509) may be added to photographic emulsions to act as spreading agents in the preparation of multiple coatings.

Mannitan monolaurate (467, 519), polyglycerol laurate (461), and dioxanediol esters (510, 511) have been suggested as ingredients of insecticide compositions. Their function is to allow rapid spreading of insecticides without permitting penetration in depth. Mannitan monolaurate, by itself, has been stated to have insecticidal power. It reduces the inhibiting effect of greenhouse sprays on the photosynthesis of the plants thus treated (422).

Polyglycerol esters are suggested as additives to dry-cleaning solvents (456).

In general, the following materials have been described to act as wetting, levelling, penetrating agents or detergents: glycol (butylene, amylene glycol) esters of short-chain acids up to lauric acid (173, 192, 496); diethylene and triethylene glycol esters (192, 233, 237, 496); polyglycol esters (192, 199, 237, 275, 278, 279, 302, 305a, 355, 358a, 362a, 488); glycerol esters (69, 192, 233, 237, 289, 412a, 496); polyglycerol esters (160, 161, 192, 233, 236, 238, 276, 228); erythritol, pentitol, hexitol, and saccharide esters (63, 228, 467); esters of hydroxyalkyl ethers of polyhydric alcohols (274, 288, 295, 308, 412b, 486, 487).

A comparatively novel application for a surface-active agent is as an anti-spattering agent, that is, to reduce the spattering of shortenings or margarine during frying. This action is not common to all polyhydric alcohol esters and is said to be most marked with a specific group of esters described as "well-balanced" hydrophilic lipins. However, the recorded materials include propylene and ethylene glycol monoesters (91, 92), mono- and di-glycerides (91, 92, 159, 168, 374), diglycerol esters (91, 92), polyglycerol esters (160, 161, 168, 228, 229, 236, 238, 231, 232, 276), hexitol esters and sugar esters (105, 159, 163, 168, 228, 229, 231, 232).

Polyhydric alcohol esters, such as glucose, polyglycerol, sucrose, lactose, and mannitol esters (228), polyglycol esters (275, 278, 488), diglycerol, propylene glycol, and ethylene glycol monolaurate, glycerol monostearate, glycerol mono- and di-oleates (91, 92), and hydroxyalkyl glycerol esters (308) have been claimed as foaming agents. Glycerides, however, have also been stated to defoam yeast (30).

Polyhydric alcohol esters, added as such or after incorporation into shortening are said to improve pastries and other bakery products. Thus, glycerides may be added to the flour (110, 451) or to the shortening used (248, 433, 454, 455). Pastry of high sugar-to-flour ratio may be improved by the addition of glycerides (109, 111, 112, 113, 116, 117, 118, 119, 146, 186, 226, 246, 247, 430, 435, 436, 437, 446, 453, 454, 455, 529, 530). Other polyhydric alcohol esters suggested for the improvement of pastry are polyglycerol esters (110, 162, 186, 226, 247, 431, 451), sugar alcohol or sugar esters (110, 226, 431, 451), and even diethylene glycol esters (248). It should be noted that the addition of glycerol monostearate to cake was recently found to make little difference except for an increased volume index (126). Polyhydric alcohol esters will prevent dough from sticking to baking tins (146). Shortenings for baking and other purposes are said to be improved by the incorporation of mono- and di-glycerides (108, 109, 114, 115, 157, 167, 186, 246, 248, 372, 428, 429, 453, 471), polyglycerol esters (147, 432) and other polyhydric alcohol esters (248).

Among the most outstanding applications of partial fatty acid esters of polyhydric alcohols is their stabilizing action for certain water-in-oil emulsions, particularly margarine. For this, polyhydric alcohol esters are added to suitable mixtures of oils and hydrogenated oils, and milk is added with agitation until it is properly emulsified in the oils. Chiefly, two types of stabilizers for this purpose have been recommended: first, mono- and di-glycerides of fatty acids, which may be used as such or together with small amounts of soap or of free fatty acids (99, 100, 146, 160b, 163, 164, 226, 230, 234, 239, 335, 396, 398, 471, 496); polyglycerol esters (161, 163, 415, 489), glycol and diethylene glycol esters (160b, 248, 398, 496), sugar alcohol and sugar esters (160a, 160b, 245), and other polyhydric alcohol esters (192, 227, 398) have also been suggested. Monoglycerides may be used to help stabilize salad dressings (30, 471) or other water-in-oil emulsions (564). The second type of stabilizer is obtained by the esterification or reësterification of polymerized and (or) oxidized fatty acids or oils with polyhydric alcohols, such as glycerol, erythritol, hexitols, glycol, polyglycerol, or sugars (168, 373, 374, 489, 490, 491, 492, 493, 494, 495).

The use of diglycerides in conjunction with lecithin has also been described (166).

While polyhydric alcohol esters are useful water-in-oil emulsifiers under certain conditions, these same esters may also be used as oil-in-water emulsifiers. The conditions under which they are used determine the type of the resulting emulsion. In general, it appears that oil-in-water emulsions will result if the polyhydric alcohol esters are, by themselves, readily enough dispersible in water, or are used in conjunction with stabilizers more water soluble than they themselves. Such stabilizers are, in particular, alkali, ammonium, and amine soaps, or chemicals forming them *in situ*, but also wetting agents like the aryl alkyl sulfonates (199), sulfonated fatty alcohols (199, 498), sulfonated oils or sulfonated monoglycerides (237, 306), the cationic "Sapamines" (191b, 193, 194, 443, 444, 472), the non-ionic condensation products of decomposed proteins with fatty acids (198, 497), or the sulfosuccinates (199).

There are, of course, all kinds of emulsions, and their applications are very numerous. Certain specific uses, however, have been recorded in the literature, and may be briefly reviewed:

Petroleum-base insecticidal sprays are widely used in agriculture. They are usually emulsifiable oils which yield comparatively coarse and unstable milks with water. This instability is desirable as a means of protecting the foliage, and, in fact, emulsion breakers are suggested to insure quick breakdown. Examples of such materials are aluminum soaps. Other ingredients of these emulsions are amine soaps or mahogany soaps. Glycol esters (6, 344, 345, 346, 502), diethylene glycol esters (410, 411), triethylene or tetraethylene glycol esters (196, 412), mono- and di-glycerides (6, 343, 344, 345, 346, 347, 348, 502, 559), mannitan (467, 519), polyglycerol (461), and dioxanediol esters (510, 511) have been recommended as emulsifiers.

Detergent as well as lubricating (softening) action is required in washing wool. For this, glycol (496, 568) or polyglycol esters (275, 302, 488) may be used.

To get a one-bath waterproofing process, aluminum salt solutions are added to cold aqueous dispersions of glycol or diethylene glycol esters. Waterproofing results on hot-calendering of the treated cloth (106).

Kerosene or dichlorobenzene, emulsified by borax and diethylene glycol esters, serves as a radiator flush (340).

Linseed oil dispersed by polyethylene glycol esters may be used in the fat liquoring of leather (275).

Polyethylene glycol esters (277) serve as emulsifiers for resins dissolved in naphtha, for ink.

Diethylene glycol esters (567) or mono- and di-glycerides (506) give polishes when emulsified with soap, mineral oil or naphtha, and water.

Monoglycerides (102) have been suggested as stabilizers for heterogeneous reactions.

A very large percentage of all emulsions is used for creams, lotions, and other cosmetic products; hence it is not surprising that many emulsifiers have been suggested for this purpose. Glycol esters will disperse to form good creams, salves, or lotions (70, 71, 72, 101, 244, 251, 255, 356, 427, 434, 472, 524, 557, 560, 568, 571). Propylene glycol esters, particularly in conjunction with amine soaps, make good suppositories and other water-absorbing bases (49, 50, 91, 92). Pentanediol oleate has been recommended for shaving compositions (251). Diethylene glycol esters have been suggested for various cosmetic purposes (17, 18, 71, 242, 320, 325, 356, 570, 571). Polyethylene glycol esters are also suitable (199, 242). Diglycol stearate, together with sulfated hydrogenated castor oil, petrolatum, and water, will give a satisfactory base for ointments (175). Mono- and di-glycerides are widely recommended as cosmetic emulsifiers, such as for petrolatum ointments (389), for toothpastes (17), and for other purposes (27, 101, 188, 195, 244, 289, 320, 325, 328, 335, 356, 361, 387, 412a, 427, 434, 442, 445, 472, 475, 476, 496, 557, 569, 570, 571); polyglycerol esters are used similarly (243, 244, 361).

Textile sizing or lubrication may be accomplished with mineral or vegetable oils emulsified by diethylene glycol esters (125) or polyethylene glycol esters (275).

Vitamin-containing oils may be emulsified by polyglycerol monoesters (24), hexitol, or sugar esters (169).

In general, the majority of polyhydric alcohol esters have been recommended for emulsification. This includes the esters of glycol (31, 32, 91, 92, 146, 192, 197, 419, 496), glycol and glycerol (195, 404, 463), diethylene glycol (29, 31, 32, 71, 146, 196, 243, 257, 403, 496), polyglycols (34, 199, 200, 275, 302, 496), and glycerol (30, 33, 74, 75, 80, 91, 92, 99, 100, 103, 146, 191a, 192. 195, 197, 203, 257, 276, 289, 330, 332, 333, 335, 390, 403, 412a, 447, 457, 458, 478, 479, 496, 548), and also the esters of the polyglycerols (33, 34, 74, 91, 92, 147, 226, 236, 238, 242, 243, 264, 303, 305a, 393, 432), of hydroxyalkyl ethers of polyhydric alcohols (274, 288, 412b, 487), of pentaerythritol (33, 34), of erythritol (203), of hexitols such as mannitol or sorbitol (33, 34, 168, 203, 242, 243, 245, 323, 572), and of sugars, such as glucose or sucrose (60, 168, 245, 484).

Soaps blended with polyhydric alcohol esters are suitable as additions to hair-waving solutions (127). Glycol monoesters (496), diethylene glycol esters (29), and polyglycerol esters (236) may be used for the "superfatting" of soaps.

Polyhydric alcohol esters of higher aliphatic hydroxycarboxylic acids may be used as electric insulators (310) or to fill radio condensers (146). At the same time, glycol, glycerol, and other polyhydric alcohol partial esters, together with fatty acid alkylol amides, have been suggested for use in overcoming difficulties due to the static electricity of synthetic (cellulose ester or ether) yarns or films (137, 138).

Glycol, glycerol, or polyglycerol ricinoleates have been suggested for use in the breaking of crude petroleum emulsions (128, 423). Glycol oleate and glycerol monoricinoleate are suggested as ingredients of oil-well drilling fluids of low "gas cutting" tendencies (327).

Certain monoglycerides are said to prevent rancidity in shortenings (78, 79).

Glycol esters of the odd-numbered fatty acids have been suggested as food in certain diabetic diets (384). Palmitates of propylene glycol and trimethylene glycol activate the action of testosterone (261, 408, 409). Mono- and di-glycerides or glycol monoesters, emulsified with skimmed milk, have been suggested as a live-stock food in place of butter fat removed as cream (98).

Mono- and di-glycerides may be reacted with acidic unrefined oils to remove their free fatty acids. Advantages of this method over that of using glycerol are ready miscibility, quick reaction, and minimum formation of partial esters (67, 513).

Small amounts of glycerol monostearate are stated to eliminate "sun-checking" of butadiene synthetic rubbers (125). The sticking together of raw rubber sheets can be overcome by spraying wich a diethylene glycol stearate dispersion, which is absorbed in processing later on (125).

In closing this review, the attention of the reader is drawn to a recently published compilation of surface-active agents commercially available in the United States (26), which contains references to numerous polyhydric alcohol esters.

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